UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

2014-1209

CREAGRI, INC., a California Corporation,

PLAINTIFF-APPELLANT,

V.

PINNACLIFE, INC., a Nevada Corporation,

DEFENDANT-APPELLEE.

APPEAL FROM THE UNITED STATES DISTRICT COURT FOR THE NORTHERN DISTRICT OF CALIFORNIA IN CASE NO. 11-cv-06635-LHK, Judge Lucy H. Koh

BRIEF FOR PLAINTIFF-APPELLANT CREAGRI, INC.

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CERTIFICATE OF INTEREST

Counsel for Plaintiff-Appellant, CreAgri, Inc., certifies the following:

1. The full name of every party represented by us is:

   CreAgri, Inc.

2. The name of the real party in interest represented by us is:

   CreAgri, Inc.

3. All parent corporations and any other publicly held companies that own 10 percent or more of the stock of the party or *amicus curiae* represented by me are:

   None.

4. The names of all law firms and the partners or associates that appeared for CreAgri, Inc. in trial court or are expected to appear in this court are:

   Paul J. Andre, Lisa Kobialka, and Hannah Lee of Kramer Levin Naftalis & Frankel LLP.

Dated: March 10, 2014 */s/Paul J. Andre*

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STATEMENT OF RELATED CASES

Pursuant to Fed. Cir. Rule 47.5(a), CreAgri, Inc. ("CreAgri") states that no appeal other than the current appeal has been taken, in or from, the same civil action or proceeding in the District Court. There are no other pending cases between the parties to this appeal.

STATEMENT OF JURISDICTION

The Honorable Lucy Koh of the United States District Court for the Northern District of California ("District Court") had jurisdiction over Plaintiff CreAgri's patent infringement action below under 28 U.S.C. §§ 1331 and 1338.

On December 18, 2013, the District Court issued an Order granting Pinnaclife's Motion for Summary Judgment of Invalidity. JA2-38. On January 3, 2014, the District Court entered final judgment in favor of Defendant Pinnaclife. JA1.

CreAgri filed a timely notice of appeal on January 2, 2014. JA3323-24; JA3325-26. This Court has jurisdiction over this appeal under 28 U.S.C. § 1295.

STATEMENT OF THE ISSUES PRESENTED FOR REVIEW

The issue presented in this appeal is whether the District Court erred in determining that U.S. Patent Nos. 6,416,808 ("the '808 Patent") and 8,216,599 ("the 599 Patent") (collectively, the "Asserted Patents") are invalid. More specifically:

1. Did the District Court err in its construction of the term "aqueous extract of olives" in the claims of the '808 Patent?

2. Did the District Court err in granting Pinnaclife, Inc.'s ("Pinnaclife") Motion for Summary Judgment of Invalidity that the asserted claims of the '808 Patent are invalid pursuant to 35 U.S.C. § 102?

3. Did the District Court err in granting Pinnaclife's Motion for Summary Judgment of Invalidity that the asserted claims of the '599 Patent are invalid for failure to meet the written description requirement of 35 U.S.C. § 112(a) and for lack of enablement and utility under 35 U.S.C. §§ 101 and 112(a)?

STATEMENT OF THE CASE

On December 23, 2011, CreAgri brought this patent infringement action in the United States District Court for the Northern District of California. JA93-110. In its Complaint, it asserted that Pinnaclife infringed certain claims of the Asserted Patents that are directed towards olive-derived products or methods of using the same to treat inflammatory conditions. JA470-546. The District Court granted Pinnaclife's Motion for Summary Judgment of Invalidity on the papers ("Order"), and entered judgment that the asserted claims of the '808 Patent and '599 Patent were invalid ("Judgment"). JA1; JA2-38 (*CreAgri, Inc. v. Pinnaclife, Inc.*, 11-CV-6635-LHK, 2013 WL 6673676 (N.D. Cal. Dec. 18, 2013)). In the Order, the District Court held that CreAgri's Motion for Summary Judgment of Infringement was moot, and Pinnaclife's counterclaims for declaratory judgment of noninfringement and unenforceability of the '808 Patent were dismissed without prejudice. JA2-38. This appeal of the District Court's Order and Judgment followed.

STATEMENT OF FACTS

A. The Parties

1. Plaintiff CreAgri and Its Patented Products

Plaintiff CreAgri was founded in 1999 and is a small, nutraceutical company with its headquarters in Hayward, California. Dr. Roberto Crea, the founder of CreAgri has numerous patents, including the Asserted Patents, that cover products and methods related to CreAgri's olive-derived HIDROX® products. CreAgri's HIDROX® products are sold in dietary supplements, skincare products, and other applications worldwide.

2. Defendant Pinnaclife and the Accused Products

Defendant Pinnaclife, Inc. is a company with is headquarters in Coralville, Iowa. Dr. Darlene McCord founded Pinnaclife in 2009, and is one of many companies in the nutraceutical industry owned by Dr. McCord. Pinnaclife has sold and currently sells the accused olive-derived products, including dietary supplements, skincare products, and pet care products, under the brand names, Olivamine™ and Olivamine^{10}™.

B. The Asserted Patents

1. The Conception of the Patented Inventions

Generally, the production of olive oil involves the crushing of olives, including the pits, to generate oil. (*See* Figure 1 below). During the manufacturing process, a considerable amount of water is generated that, for centuries, no one

believed had any useful value or potential. Such water was commonly referred to as "olive mill waste water" because it was, in fact, historically perceived as "waste." In Europe, it was known as "black water" because it was a pollutant and costly to get rid of. As a result, the focus of the olive business was on the oil, not on the "waste water."

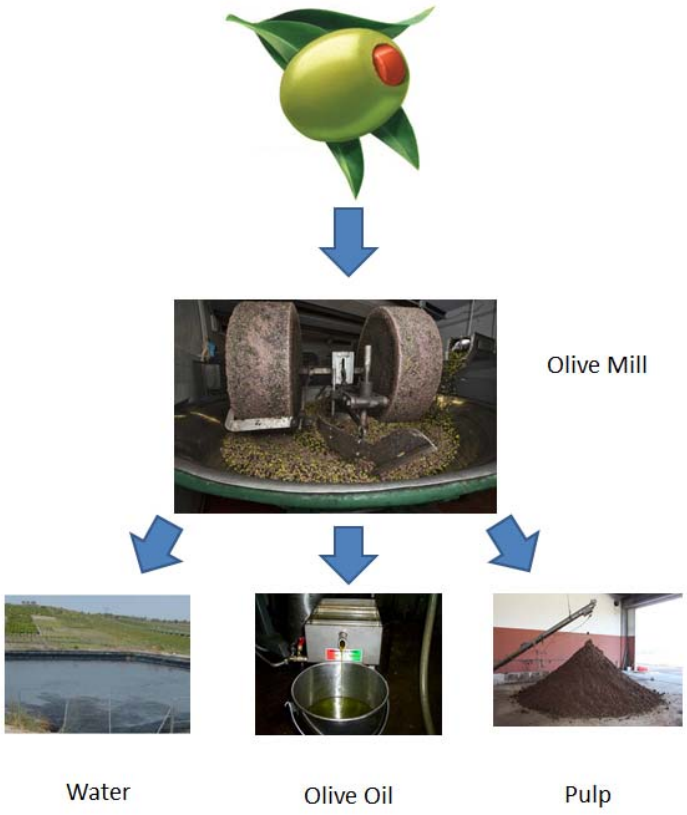

Figure 1: The processing of olives to make olive oil.

CreAgri was one of the first companies to separate olive vegetation water or "waste water" from the manufacturing process, and explore its possible benefits. In 1999, Dr. Crea began testing the "waste water" for possible use as an agricultural pesticide. JA1153-55 at 32:2-39:21. In early 2000, Dr. Crea contacted

a testing facility, called Chemiservice S.A.S. ("Chemiservice") to perform testing of weight ratios of hydroxytyrosol and oleoeuropein in vegetation water from olives after the addition of acid. JA1157 at 60:8-61:5. Between approximately February and May 2000, Dr. Crea tested and analyzed different samples for particular phenolic ratios, and obtained the claimed phenolic ratios disclosed in the '808 Patent no later than May 8, 2000. *Id.*; JA1158-59 at 108:4-112:10. With the addition of acid to the aqueous fractions, he obtained high concentrations of hydroxytyrosol in the vegetation water extract, a phenolic compound well-known for its significant antioxidant properties. JA76-77 at 8:55-9:39.

Approximately a year later, Dr. Crea performed multiple studies to detect the anti-inflammatory effect, toxicity, antioxidant capability, and other beneficial effects of using CreAgri's HIDROX® extracts. By June 15, 2001, he developed a clinical protocol to study the anti-inflammatory effect of Olivenol™, containing HIDROX®, on persons having HIV-associated dementia. JA2416-17 at ¶ 52. At the time he filed the '599 Patent application on February 13, 2003, he had performed the study and obtained favorable initial results from the study. JA3343-86 at JA3374. These results were published in the '599 Patent. JA91 at Col.18, ll.36-39.

2. The ‘808 Patent

U.S. Patent No. 6,416,808 (“the ‘808 Patent”), entitled “Method of Obtaining a Hydroxytyrosol-Rich Composition From Vegetation Water,” issued to CreAgri on July 9, 2002, and has a priority filing date of September 1, 2000, the date of its provisional application. JA67-77. The ‘808 Patent contains a total of six composition claims: two independent claims (Claims 1 and 5), and four dependent claims (Claims 2-4 and 6). JA77. All claims are directed to “a dietary supplement comprising an aqueous extract of olives” containing a weight ratio of two particular compounds in olives (hydroxytyrosol, tyrosol, or oleuropein). *Id.* Dependent claims 3 and 4 are generally directed to the claimed invention as a powder, tablet, capsule, pill, or confection food additive. *Id.*

3. The ‘599 Patent

U.S. Patent No. 8,216,599 (“the ‘599 Patent”), entitled “Method for Treatment of Inflammation” issued to CreAgri on July 10, 2012, and has a priority filing date of February 13, 2002, the date of its provisional application. JA78-92. The ‘599 Patent has a total of 16 claims, eight which are asserted in this case. Independent claims 1 and 16 are generally directed to methods of treating inflammatory conditions with olive-derived extracts having ratios of hydroxytyrosol and oleuropein, substantially purified hydroxytyrosol, or a substantially purified mixture of hydroxytyrosol and oleuropein. *Id.*

The specification of the '599 Patent contains twenty columns of written disclosure describing the claimed inventions, testing, and detailed examples of embodiments of the claimed methods. It discloses analysis of biomarkers or symptoms of particular types of inflammation set forth in independent Claim 1. *See, e.g.*, JA88 at Col.11, ll.45-Col.12, ll.29 (discussing symptoms of neuropsychological testing, markers in CSF identified by methods known in the art, measurement of isoprostane F2), JA91 at Col.17, ll.4-60 (measuring CSF F2-isoprostane levels), JA91 at Col.18, l.50, Col.18, l.55, Col.18, l.61 (measuring C-reactive protein, "CRP"). It also discloses using the claimed olive-derived phenolic compounds to treat different inflammatory conditions set forth in independent Claim 16: delayed type hypersensitivity reaction (JA84, Col.4, ll.14-15; JA89, Col.13, l.50), psoriasis (JA84, Col.4, l.15, Col. 4, l.33; JA89, Col.13, l.51, Col. 13:65), autoimmune disease (JA84, Col.4, ll.16-19; JA88, Col.11, l.12, Col.12, l.39; JA89, Col.13, ll.51-54), organ transplant (JA84, Col.4, l.16; JA89, Col.13, l.51), pain (JA84, Col. 3, l.26, Col. 4:16; JA87, Col.9, ll.39-46, Col. 9, l.58; JA89, Col.13, l.35, Col. 13, l.51), fever (JA84, Col.4, l.16; JA89, Col.13, l.52), and tissue graft rejection (JA84, Col.4, l.16; JA88, Col.12, ll.36-49; JA89, Col.13, ll.48-54).

The '599 Patent specification also discloses four Examples showing the use of the claimed olive-derived compounds to treat persons suffering from various

inflammatory conditions. JA90-92 at Col.16, l.35-Col.19, l.31. Initial results were obtained for Examples 1-3. JA91 at Col.18, ll.36-39. In addition, it cites over 180 prior art references which are incorporated by reference in the specification and, as stated, "indicative of the level of skill of those skilled in the art to which the invention pertains." JA78-81; JA92 at Col.19, ll.25-31.

C. The Proceedings Below

On December 23, 2011, CreAgri filed a Complaint against Pinnaclife asserting a claim of patent infringement of the '808 Patent. JA93-110. On July 30, 2012, CreAgri filed an Amended Complaint to add a claim of patent infringement of the '599 Patent. JA126-62. On January 22, 2013, CreAgri filed a Second Amended Complaint amending its indirect infringement claims related to the '599 Patent. JA470-546.

1. The District Court Construed Disputed Claim Terms of the Asserted Patents

On April 16, 2013, the District Court issued an order construing seven disputed terms of the Asserted Patents. JA38.01-38.44. In the '808 Patent, the term "aqueous extract of olives" was construed as ""an aqueous solution containing a water-soluble preparation from an olive plant,' with no restriction on the process by which the 'aqueous solution' is obtained." JA38.32.

2. The District Court Granted Pinnaclife's Motion for Summary Judgment of Invalidity

On September 19, 2013, CreAgri filed a Motion for Summary Judgment of Infringement, and Pinnaclife filed a Motion for Summary Judgment of Invalidity. On December 18, 2013, the District Court issued an Order granting Pinnaclife's Motion for Summary Judgment of Invalidity. JA2-38. Specifically, the District Court held that all claims of the '808 Patent was anticipated by U.S. Patent No. 6,358,542 ("Cuomo") and/or an article entitled, "Polyphenolic Content in Five Tuscany Cultivars of *Olea europaea* L." ("Romani"). JA2, JA14, JA17; JA1029-47; JA981-84. In its Order, it construed the term "aqueous extract of olives" to include aqueous-alcoholic extracts of olives. JA13. The District Court also held that all claims of the '599 Patent were invalid for lack of written description under 35 U.S.C. § 112(a), and invalid for lack of enablement and utility under 35 U.S.C. §§ 101 and 112(a). JA37.

a. The District Court Held Cuomo Anticipates Claims 1-5 of the '808 Patent

The District Court found that the only disputed limitation in the Cuomo disclosure was the presence of "an aqueous extract of olives." JA10. However, it found Example 11 in Cuomo contained that limitation: "Example 11's description of an 80% *aqueous* methanol solution comprising the dissolved olive pulp from Example 4 plainly describes an 'aqueous solution containing a water-soluble

preparation from an olive plant,' and therefore no reasonable jury could conclude that the reference fails to disclose the 'aqueous extract of olives' limitations of claims 1 through 5 of the '808 Patent." JA11. It held that the following "key" passage of the specification of the '808 Patent "makes clear that the invention includes—rather than excludes—the use of aqueous-alcoholic extracts."

> The hydroxytyrosol obtained by the method *of the invention* can be administered orally or parenterally. Oral dosage forms can be in a solid or liquid form. Such dosage forms can be formulated from purified hydroxytyrosol *or they can be formulated from aqueous or aqueous-alcoholic extracts*. Regarding the latter, aqueous or aqueous-alcoholic (e.g. water-methanol or water-ethanol) extracts can be spray-dried to provide a dry powder that can be formulated into oral dosage forms with other pharmaceutically acceptable carriers. The *aqueous or aqueous-alcoholic extracts* can be formulated to contain various weight ratios of hydroxytyrosol to oleoeuropein of between 5:1 and 200:1, preferably between about 10:1 and about 100:1. *The extracts* may also be formulated to contain various weight ratios of hydroxytyrosol and tyrosol of between about 3:1 and about 50:1, preferably between about 5:1 and about 30:1.

JA12; JA76 at Col.7, ll.41-56 (emphases added in Order). It specifically stated, "to avoid any doubt, the Court holds that its construction of 'aqueous extract of olives' encompasses 'aqueous-alcoholic extracts.'" JA13.

b. The District Court Held Romani Anticipates Claims 1, 2, 5, and 6 of the '808 Patent

The District Court also held that Romani discloses "an intermediate step in which the weight ratios of polyphenolic compounds claimed in the '808 Patent exist in an 'aqueous solution.'" JA15. More specifically, it stated that "Romani

recounts a procedure in which the authors took olive pulps frozen in liquid nitrogen, ground them, and then used ethanol to extract the wanted polyphenols." *Id.* It then described Romani's authors concentrating the ethanolic extract and rinsing it with acid water to form an "aqueous solution" that was "defatted" into a concentrated "aqueous phase." *Id.* The District Court found that the intermediate "aqueous solution" and "aqueous phase" satisfy the "aqueous extract" limitation of the '808 Patent claims, and stated "[t]he premise of this procedure is that the intermediate steps in the measurement process (during which the authors obtain the aqueous extract of olives) do not alter the hydroxytyrosol, tyrosol, and oleuropein levels naturally found in the Rossellino cultivar, levels that indisputably fall within the ratios stated in claim 1-2 and 56 [*sic*] of the '808 Patent." JA16. Both parties agreed that claims 3 and 4 have limitations that were not anticipated by Romani, so the District Court did not find Romani anticipated those claims. JA17.

c. The District Court Held The '599 Patent Lacks Written Description under 35 U.S.C. § 112

The District Court found that all claims of the '599 Patent were invalid for lack of written description. JA18. Specifically, it held that the specification of the '599 Patent did not "explain why the inventor believed that the hydroxytyrosol and oleuropein compositions recited in the claims would counteract any of the listed causes of inflammation." JA22. The District Court cited a single excerpt of the inventor's deposition testimony stating applications for patents could be

"prophetic." JA20-21. It further found that all the examples in the '599 Patent were "prophetic" and the disclosed studies were only proposals that did not "demonstrate the efficacy of the therapy." *Id.* at 22-23. It also held that the study JA23-24 the first three examples used a sample size ("up to 32 subjects") that was too small to support the "effectiveness of the patented therapy as to the full scope of the claims." JA24.

The District Court also held that the '599 Patent did not "inherently" satisfy the written description requirement because the disclosure of relevant biomarkers did not show "how to measure whether the claimed treatment works." JA25-26. It held that the CreAgri's expert, Dr. German, only showed that the '599 Patent inherently discloses "how to measure *whether* the treatment works as claimed, not that the treatment *does* work as claimed." JA26. It also found that five prior art references incorporated into the specification of the '599 Patent did not "demonstrate the medical efficacy of hydroxytyrosol, hydroxytyrosol together with oleuropein, or olive plant extract having a given ratio of hydroxytyrosol to oleuropein, for treating inflammation arising out of the numerous causes recited in the claims of the '599 Patent." *Id.*

d. The District Court Held The '599 Patent Lacks Enablement and Utility under 35 U.S.C. §§ 101 and 112(a)

In holding the '599 Patent was not enabled, the District Court, in its Order, cited to an unsworn statement of Pinnaclife's expert that "by 2002, no researcher working in the field of olive-derived polyphenols had published reliable data establishing that either hydroxytyrosol or oleuropein showed *in vivo* anti-inflammatory activity," and "[i]n the 1999-2002 time period, anti-inflammatory activity could not be inferred from research showing that olive-derived polyphenols exhibit antioxidant activity." JA30. The District Court held this was "clear and uncontroverted evidence." *Id.* Pinnaclife did not cite these statements of its expert in its briefs to the District Court in support of its Motion for Summary Judgment. JA832-63; JA2785-803.

CreAgri's expert refuted Pinnaclife's expert's statements, but the District Court found that CreAgri's expert's statements did not create an issue of material fact, and his citation of two prior art references "[did] not support the notion that a person of ordinary skill in the art would accept without question that the claimed olive-derived phenolic compounds would have the claimed therapeutic effects." JA32. The District Court also found five additional prior art references incorporated in the specification do not show that "a person of ordinary skill in the

art would not accept without question the effectiveness of the claimed therapies in treating ailments listed in the claims." *Id.*

It also found that post-filing data in two published articles of the studies disclosed in the '599 Patent could not support utility. Specifically, it held that the first publication "explicitly disclaims the anti-inflammatory effects of hydroxytyrosol," and the second study could not enable the full scope of the '599 Patent claims in treating "coronary, bronchial, and neuro inflammation (claim 1) and inflammation from psoriasis, organ transplant, fever, and tissue graft rejection (claim 16)." JA33-34. It also held that the specification of the '599 Patent "[did] not explicitly provide any analytic reasoning as to why the invention would work as claimed." JA36.

REPRESENTATIVE CLAIMS

CreAgri asserted Claims 1-6 of the '808 Patent against Pinnaclife ("the Asserted Claims"). Claims 2-4 depend from independent Claim 1, which is reproduced below.

> 1. A dietary supplement comprising an aqueous extract of olives containing a weight ratio of hydroxytyrosol to oleoeuropein of between about 5:1 and about 200:1.

JA77 at Col.10, ll.36-38. Claim 6 depends from independent Claim 5, reproduced below.

> 5. A dietary supplement comprising an aqueous extract of olives containing a weight ratio of hydroxytyrosol and tyrosol of between about 3:1 and about 50:1.

Id. at Col.10, ll.48-50.

CreAgri asserted Claims 1, 2, 4-5, 12-14, and 16 of the '599 Patent against Pinnaclife ("the Asserted Claims"). Claims 2, 4-5 and 12-14 depend from independent Claim 1, which is reproduced below.

> 1. A method of treating a subject having an inflammatory condition characterized by a detectable clinical symptom or change in a level of a biochemical marker with respect to the normal range of the marker, the method comprising:
>
> administering to the subject a dose corresponding to between about 0.1 mg/kg body weight and 2000 mg/kg body weight daily of a first treatment agent comprised of an olive plant extract having a weight ratio of hydroxytyrosol to oleuropein of between about 1:1 and about 200:1; and
>
> continuing said administration until there is observed a return of the marker level to the normal range or a desired change in the clinical symptom,
>
> where the marker of the clinical symptom is selected from the group consisting of:
>
> (i) elevated levels of C-reactive protein in the case of coronary inflammation;
>
> (ii) respiratory distress in the case of bronchial inflammation; and
>
> (iii) elevated CSF levels of isoprostanes or clinical symptoms determined from neuropsychological testing in the case of neuro inflammation.

JA92 at Col.19, ll.36-Col.20, ll.1-5. Independent Claim 16 of the '599 Patent is reproduced below:

> 16. A method of treating an inflammatory condition in a subject in need of such treatment, comprising administering to said subject a dosage amount corresponding to between about 0.1 mg/kg body weight and 2000 mg/kg body weight daily of substantially purified hydroxytyrosol or a substantially purified mixture of hydroxytyrosol and oleuropein, wherein said inflammatory condition is in response to a condition selected from the group consisting of: delayed type hypersensitivity reaction, psoriasis, an autoimmune disease, organ transplant, pain, fever, and tissue graft rejection.

Id. at Col.20, ll.42-51.

SUMMARY OF ARGUMENT

The District Court committed multiple errors of law and fact in granting Defendant Pinnaclife's Motion for Summary Judgment of Invalidity. First, the District Court erred in its construction of the claim term "aqueous extract of olives," the basis for its grant of summary judgment of invalidity of the '808 Patent. Its construction is illogical and inconsistent with the intrinsic record.

In the '808 Patent's specification, the inventor noted that embodiments of the invention could be made from aqueous *or* aqueous-alcoholic extracts of olives. In the claims, however, the inventor chose to limit the claims to only the "aqueous extract of olives" and did not claim compositions directed to the aqueous-alcoholic extracts of olives. JA77 at Col.10, ll.35-54. In its Order granting summary judgment, the District Court determined that, based on the embodiments in the

specification, the term "aqueous extract of olives" also includes aqueous-alcoholic extracts. JA13 ("to avoid any doubt, the Court holds that its construction of 'aqueous extract of olives' encompasses 'aqueous-alcoholic extracts.'")

As the District Court's construction is incorrect as a matter of law and the '808 Patent is valid under the correct construction of "aqueous extract of olives," the grant of summary judgment of invalidity of the '808 Patent should be reversed.

Even if the District Court's claim construction is not reversed, the grant of summary judgment of invalidity against the '808 Patent should be reversed because the prior art does not teach an aqueous or an aqueous-alcoholic extract of olives. Both prior art references teach analysis of alcohol extractions from the olive. Therefore, even under the District Court's flawed construction of "aqueous extract of olives" to include aqueous-alcoholic extracts, the prior art does not disclose the analysis of compositions derived from aqueous or aqueous-alcoholic extracts of olives.

With respect to the '599 Patent, the District Court erred by confusing the written description, enablement, and utility requirements for patents with the efficacy requirement for drug approval from the U.S. Food and Drug Administration ("FDA"). There was no finding that the '599 Patent's specification failed to describe or enable the treatment of inflammation using the claimed compounds. Instead, the District Court found that the specification failed to show

medical proof that using the claimed compounds to treat inflammation was effective. Because the District Court used the incorrect standards under 35 U.S.C. §§ 101 and 112, and there were disputed material issues of fact, its finding of invalidity should be reversed.

ARGUMENT

A. Standard of Review and Applicable Law

This Court reviews the grant of summary judgment *de novo,* applying the same legal standards as the District Court, and drawing all reasonable inferences in favor of the non-moving party. *Ohio Willow Wood Co. v. Alps South, LLC*, 735 F.3d 1333, 1341-42 (Fed. Cir. 2013). Summary judgment is appropriate only when there is no genuine issue of material fact and the moving party is entitled to judgment as a matter of law. Fed. R. Civ. P. 56(a), (c). To defeat summary judgment, CreAgri needed only to have come forward with sufficient evidence that, when construed in its favor, a reasonable jury could find for it. *Vita-Mix Corp. v. Basic Holding, Inc.*, 581 F.3d 1317, 1323 (Fed. Cir. 2009). The party challenging the patent bears the burden of proving invalidity by clear and convincing evidence. *Motorola Mobility, LLC v. Int'l Trade Com'n*, 737 F.3d 1345, 1348 (Fed. Cir. 2013).

Anticipation and compliance with written description are questions of fact. *Id.*; *Trading Techs. Int'l, Inc. v. Open E Cry, LLC*, 728 F.3d 1309, 1318 (Fed. Cir.

2013). Also, "[w]hether an application discloses a utility for a claimed invention [under 35 U.S.C. § 101] is a question of fact." *In re Fisher*, 421 F.3d 1365, 1369 (Fed. Cir. 2005).

Enablement is a question of law reviewed by this Court based on underlying factual inquiries reviewed for clear error. *Cephalon, Inc. v. Watson Pharms., Inc.*, 707 F.3d 1330, 1336 (Fed. Cir. 2013). A patent is presumed enabled, and the challenger bears the burden, throughout the litigation, of proving lack of enablement by clear and convincing evidence. *Id.* at 1337 (citing *Morton Int'l, Inc. v. Cardinal Chem. Co.*, 5 F.3d 1464, 1469-70 (Fed. Cir. 1993)). "[Enablement] is met when at the time of filing the application one skilled in the art, having read the specification, could practice the invention without "undue experimentation." *Cephalon*, 707 F.3d at 1336 (citing *In re Wands*, 858 F.2d 731, 736-37 (Fed. Cir. 1988)). The focus "is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance." *PPG Indus., Inc. v. Guardian Indus. Corp.*, 75 F.3d 1558, 1564 (Fed. Cir. 1996)(citation omitted).

B. The District Court Erred In Its Construction Of "Aqueous Extract of Olives."

Claim construction is an issue of law that this Court reviews *de novo*. *Nazomi Comm'ns, Inc. v. Nokia Corp.*, 739 F.3d 1339, 1343 (Fed. Cir. 2014). This Court should reverse the District Court's construction of the claim term "aqueous

extract of olives" because it erred when it ignored the plain language of the claim. Specifically, the District Court erred by construing "aqueous extract of olives" to encompass aqueous extracts ***and*** aqueous-alcoholic extracts. This erroneous construction, provided at the time of its Summary Judgment Order, was the sole basis for the District Court's finding that the claims of the '808 Patent were anticipated by the two prior art references.

On April 16, 2013, the District Court initially construed the term "aqueous extract of olives" to be ""an aqueous solution containing a water-soluble preparation from an olive plant,' with no restriction on the process by which the 'aqueous solution' is obtained." JA38.32. Eight months later, on December 18, 2013, in its Summary Judgment Order, the District Court amended its construction of "aqueous extracts" to include "aqueous-alcoholic extracts." JA13. The District Court's construction is erroneous because it is in direct contradiction to the intrinsic record.

The term "aqueous-alcoholic" appears in two different sections of the specification of the '808 Patent. JA76 at Col.7, ll.42-53, Col.8, ll.6-10. Each time it appears in the specification, the patentee clearly distinguished between "aqueous-alcoholic" and "aqueous" extracts.

> Such dosage forms can be formulated from purified hydroxytyrosol or they can be formulated from aqueous ***or*** aqueous-alcoholic extracts. Regarding the latter, aqueous ***or*** aqueous-alcoholic (e.g., water-methanol or water-ethanol)

> extracts can be spray-dried to provide a dry powder that can be formulated into oral dosage forms with other pharmaceutically acceptable carriers. The aqueous ***or*** aqueous-alcoholic extracts can be formulated to contain various weight ratios of hydroxytyrosol to oleoeuropein of between 5:1 and 200:1, preferably between about 10:1 and about 100:1.

Id. at Col.7, ll.42-51 (emphasis added).

> Alternatively, the hydroxytyrosol obtained in accordance with this invention for oral administration can be in liquid form wherein the pharmaceutically acceptable carrier is water ***or*** an aqueous-alcoholic medium.

Id. at Col.8, ll.6-10 (emphasis added).

The inventor's use of the disjunctive term "**or**" evidences that he clearly intended there to be a marked difference between the two. *See SkinMedica, Inc. v. Histogen Inc.*, 727 F.3d 1187, 1199 (Fed. Cir. 2013)("[t]he disjunctive 'or' plainly designates that a series describes alternatives"); *see also Joy MM Delaware, Inc. v. Cincinnati Mine Machinery, Co.*, 497 Fed. Appx. 970, 973 (Fed. Cir. 2012) (inventor's use of the disjunctive "or" indicates that he appreciated the commonly understood meaning of the term as exclusive of the other). In the '808 Patent, the inventor was clear to state that dosage forms can be obtained either using "aqueous ***or*** aqueous-alcoholic (*e.g.* water-methanol or water-ethanol) extracts." JA76 at Col.7, ll.45-46 (emphasis added); *see also id.* at Col.8, l.9 ("water ***or*** an aqueous-alcoholic medium) (emphasis added).

Thus, in every instance in the '808 Patent, the patentee used clear and unmistakable language to distinguish between "aqueous" and "aqueous-alcoholic." When a patentee has clearly distinguished the meaning of a term, this Court has given the meaning accorded by the patentee. *See SkinMedica*, 727 F.3d at 1197, 1200, 1202 (holding term culturing "in three dimensions" excluded culturing "with beads" when patentees plainly and repeatedly distinguished the two in the specification particularly by use of disjunctive phrase "or"); *see also Bell Atlantic Network Servs., Inc. v. Covad Comm'ns Group, Inc.*, 262 F.3d 1258, 1271 (Fed. Cir. 2001)("when a patentee uses a claim term throughout the entire patent specification, in a manner consistent with only a single meaning, he has defined that term 'by implication'")(citing *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996)).

In the '808 Patent, the inventor specifically chose to use the "aqueous extract of olives" in the claim language, instead of the "aqueous or aqueous-alcoholic extracts" discussed in the specification. Presumably, had the inventor wanted to cover both aqueous extracts and aqueous-alcoholic extracts, he would have included both in the claim language as he clearly knew the difference between the two. *See Resonate, Inc. v. Alteon Websystems, Inc.*, 338 F.3d 1360, 1365 (Fed. Cir. 2003)("[c]ourts may not rewrite claim language based on what has been omitted from a claim, and the district court's attempt to do so here was legal error"); *see*

also Rolls-Royce, PLC v. United Techs. Corp., 603 F.3d 1325, 1335 (Fed. Cir. 2010)(holding court cannot "unreasonably broaden a specific claim term" when the specification requires a particular construction). Nonetheless, the District Court ignored the plain language of the claim and the disjunctive language in the specification and determined that the term "aqueous extract of olives" included both aqueous extracts and aqueous-alcoholic extracts. JA13 ("[T]o avoid any doubt, the Court holds that the construction of 'aqueous extract of olives' encompasses 'aqueous-alcoholic extracts.'")

The District Court's sole legal basis for ignoring the actual claim language is the following language in the specification:

> The hydroxytyrosol obtained by the method *of the invention* can be administered orally or parenterally. Oral dosage forms can be in a solid or liquid form. Such dosage forms can be formulated from purified hydroxytyrosol or *they can be formulated from aqueous or aqueous-alcoholic extracts*. Regarding the latter, aqueous or aqueous-alcoholic (e.g., water-methanol or water-ethanol) extracts can be spray-dried to provide a dry powder that can be formulated into oral dosage forms with other pharmaceutically acceptable carriers. *The aqueous or aqueous-alcoholic extracts* can be formulated to contain various weight ratios of hydroxytyrosol to oleoeuropein of between 5:1 and 200:1, preferably between about 10:1 and about 100:1. *The extracts* may also be formulated to contain various weight ratios of hydroxytyrosol and tyrosol of between about 3:1 and about 50:1, preferably between about 5:1 and about 30:1.

JA12 (emphasis added in Order); JA76 at Col.7, ll.41-56.

The District Court concluded that "this passage describes 'the invention' as a whole." JA12 (citing *Trading Techs. Int'l, Inc. v. eSpeed, Inc.*, 595 F.3d 1340, 1353-54 (Fed. Cir. 2010)). Based on "this passage" in the specification, the District Court concluded that "aqueous extract of olives" must also include aqueous-alcoholic extracts of olives.

The District Court's interpretation of "this passage" is a misreading of the specific paragraph, a misapprehension of the specification as a whole, and an incorrect application of this Court's precedent. The District Court placed unwarranted emphasis on the phrase "of the invention" in the first sentence of the paragraph noted above. It ignored, however, the first part of the sentence that states "hydroxytyrosol ***obtained by the method*** of the invention . . ." JA76 at Col.7, ll.41-56. The claims in the '808 Patent are directed only to composition claims, and not to methods to obtain hydroxytyrosol.[1] JA77at Col.10, ll.35-55. As such, the District Court's rationale that the single paragraph somehow defines "the invention as a whole" because of the inclusion of the phrase "of the invention" does not even relate to composition claims. JA12. Moreover, a plain reading of the entire paragraph makes it abundantly clear that, based on the proper use of the English language, the inventor intended to distinguish between aqueous extracts

[1] Other CreAgri's patents that issued in the same family included method claims for hydroxytyrosol-rich compositions obtained from olives.

and aqueous-alcoholic extracts. The District Court's tortured logic to conclude otherwise should not stand.

Additionally, the specification as a whole makes it clear that the composition claimed in the '808 Patent relates solely to phenol extracts obtained from water – *i.e.*, the aqueous extracts. For example, in the Summary of the Invention the inventor specifically states that the hydroxytyrosol-rich compositions are derived from the aqueous extract of olives.

> SUMMARY OF THE INVENTION
>
> In one aspect, the invention includes a method of producing a hydroxytyrosol-rich composition. The method has the steps of (a) producing ***vegetation water from olives***, . . .
>
> In one embodiment, the incubating is carried out until the ***vegetation water*** has a weight ratio of . . .
>
> The method may further include fractionating the incubated, ***vegetation water*** to separate hydroxytyrosol . . .
>
> In another aspect, the invention includes a method of producing a hydroxytyrosol-rich composition that includes the steps of (a) producing ***vegetation water from olives***; . . .
>
> ***
>
> In another aspect, the invention includes a dietary supplement comprising an ***aqueous extract of olives*** containing . . .
>
> In a related aspect the invention includes a dietary supplement comprising an ***aqueous extract of olives*** containing . . .

JA73-74 at Col.2, l.56–Col.3, l.54 (emphasis added).

Reading the specification further, in every single instance where the inventor describes the composition of the invention, the hydroxytyrosol-rich composition is derived from the aqueous extract – *i.e.*, the vegetation water. The inventor dedicated a column and a half in the specification describing the production of vegetation water, and an additional two columns to describe purification of hydroxytyrosol derived from vegetation water. JA74-76 at Col.4, l.30–Col.7, l.27. Moreover, the hydroxytyrosol-rich compositions described in every example disclosed in the specification are derived from the aqueous extract, and do not even mention using hydroxytyrosol-rich composition derived from aqueous-alcoholic extracts. Therefore, it is clear that one skilled in the art reading the specification would conclude that the term "aqueous extract of olives" means the extract from water, and not the aqueous-alcoholic extract.

Finally, even the District Court begrudgingly admits that the use of the disjunctive "or" in the specification "is ambiguous at best." JA13. CreAgri disagrees that its use of the term "aqueous ***or*** aqueous-alcoholic" creates any ambiguity about the terms having differing interpretations, but even if it did, then the District Court should have resolved the ambiguity in such a way to maintain the validity of the '808 Patent. *See Medtronic Navigation, Inc. v. BrainLab Medizinische Computersysteme GmbH*, 222 Fed. Appx. 952, 956 (Fed. Cir.

2007)(holding claims, if ambiguous, are best construed to preserve their validity)(citing *Philips v. AWH Corp.*, 415 F.3d 1303, 1327 (Fed. Cir. 2005)).

Accordingly, this Court should reverse the District Court's construction of the term "aqueous extract of olives."

C. Pinnaclife Did Not Prove By Clear and Convincing Evidence That Cuomo Anticipates Claims 1-5 of the '808 Patent

The District Court erred in finding anticipation by Cuomo based on its erroneous claim construction of the term "aqueous extract of olives" to include aqueous-alcoholic extracts. There was no finding by the District Court that Cuomo disclosed pure aqueous extracts. As discussed above, if the District Court's claim construction is reversed, then the finding of anticipation should also be reversed. However, even under the District Court's incorrect claim construction, there are material issues of fact that preclude summary judgment.

The Cuomo reference teaches the use of alcohol extracts from olive pulp to test for phenols, such as hydroxytyrosol. In the examples relied upon by the District Court's Order, Cuomo describes using the olive pulp, not the aqueous (waste water) extract, to obtain phenols. JA10 ("Cuomo describes a method for obtaining a solid antioxidant composition from an olive pulp."). The olive pulp is processed according to the method disclosed in Example 4 in Cuomo. Thereafter, the material obtained from Example 4 is further processed and used for testing in

Example 11 in Cuomo. The District Court relied exclusively on the test results disclosed in Example 11 in Cuomo for its finding of anticipation.

Specifically, Cuomo washes the pulp with water, and loads the solution on an Amberlite™ XAD column.[2] JA1041-42 at col.10, l.60–col.11, l.6. The material retained by the column is then eluted with methanol. *Id*. (*see* Figure 2 below).

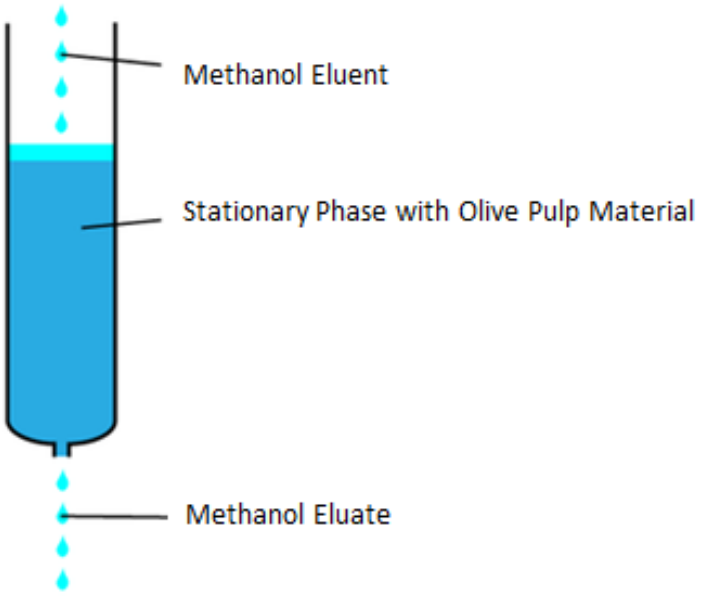

Figure 2: Olive pulp material is eluted with methanol.

[2] Column chromatography in chemistry is a method used to purify individual chemical compounds from mixtures of compounds. The individual components are retained by the stationary phase differently and separate from each other while they are running at different speeds through the column with the eluent.

In Cuomo, the methanol fraction[3] from the column is collected. JA2420-21 at ¶ 65; JA1040-45 at Col.8, ll.14-24, Col.11, ll.2-6, Col.16, l.39, Col.17, l.49. At this point in the process, Cuomo teaches that an alcohol extract from the olive pulp will be used to test for phenols. Cuomo does not teach or disclose using an aqueous or aqueous-alcoholic fraction to test for ratios of olive phenols.

In example 4 of Cuomo, after the column elution with methanol, the methanol fraction eluate is frozen. JA1042 at Col.11, l.3. Then the solid material formed in the methanol is removed by filtration, and the methanol is evaporated to yield a solid material. *Id.* at Col.11, ll.3-6. The District Court concluded that "[a]t this point, the solid antioxidant composition is not 'an aqueous extract of olives.'" JA11.

However, the District Court then concluded that the solid composition derived from the methanol fraction is somehow transformed into an aqueous extract of olives when it is dissolved in an 80% aqueous methanol solution.[4] *Id.* In other words, under the District Court's rationale, any olive extract ***derived*** from

[3] During the chromatography process the eluent is collected in a series of fractions. The stationary phase material disclosed by Cuomo, the Amberlite™ XAD, consist of polymeric adsorbents that can adsorb and then desorb a wide variety of different species depending on the environment in which they are used.

[4] The District court's sole basis for finding anticipation was that Example 11 of Cuomo cited an "80% *aqueous* methanol solution" used for dissolving the methanol fraction of the olive pulp. JA11.

any type of organic or inorganic solvent can be converted to an aqueous extract merely by processing the extract to remove the solvent to obtain a dried material, and then dissolving the dried material in an aqueous-alcoholic solution. Not only is this bad science, but it is also against the great weight of the evidence submitted by CreAgri's expert.

CreAgri's rebuttal evidence presented a genuine issue of material fact as to whether Cuomo anticipates even under the District Court's incorrect claim construction, because it presented evidence that the source material used in Example 11 of Cuomo is derived from an alcohol extract and could not be converted to aqueous after the fact. Specifically, in its Opposition to Pinnaclife's Motion for Summary Judgment, CreAgri submitted the sworn statements of its expert, Dr. Bruce German, that explained what was analyzed in Cuomo was not an "aqueous extract." JA2406-78.

Dr. German stated that, "Cuomo refers to the use of organic solvents (e.g. methanol) which are not 'aqueous extracts' (extracts from water)." JA2420-21 at ¶ 65. He explained that Cuomo analyzed the amount of phenolic compounds only after a polar aqueous filtrate from olives is first passed through a ***column*** and then rinsed with ***methanol*** (an alcoholic or organic solvent). *Id.*; JA2369. Example 11 in Cuomo takes the process one step further, and the methanolic extract is then placed in an "80% aqueous methanolic" solvent, heated, cooled, and then analyzed.

JA1043 at Col.14, ll.9-21. Dr. German testified that extracting with a methanol solvent (a type of organic solvent) is different because compounds either go into water ***or*** organic solvent. JA2370; JA2596 at 32:7-13. Thus, CreAgri submitted substantial evidence that the end-product in Cuomo obtained with multiple rounds of organic solvent was different than the claimed product of the '808 Patent that was an "aqueous extract."

The District Court recognized that CreAgri provided this uncontested evidence, but simply misapprehended the technical aspects of the evidence. For example, the District Court stated in its Order:

> CreAgri makes a half-hearted argument that Cuomo still fails to disclose the claimed "aqueous extract of olives," even under a construction of an "aqueous extract of olives" that includes "aqueous-alcoholic extracts." CreAgri relies on a declaration from its expert, Dr. Bruce German, to contend that an extract that includes methanol, such as that disclosed in Example 11, cannot be an aqueous extract. See ECF No. 118-4 at 32–33 ¶ 65 ("German Decl."). But Dr. German fails even to acknowledge that Example 11 expressly analyzes an aqueous methanol solution for phenolic content. Instead, Dr. German focuses on Cuomo's Example 4, in which the phenols are first contained in a pure methanol solution. Dr. German neglects to mention that in Example 11 those phenols are dissolved in an aqueous methanol solution, a solution that Cuomo elsewhere expressly describes as a "polar aqueous solvent."

JA13.

As demonstrated above, the District Court did not appreciate that when the column was eluted with methanol in Example 4, the result is an alcohol extract that

is the source material for Example 11. JA1041-42 at Col.10, l.60-Col.11, l.6; JA1043 at Col.14, l.13. In Example 11, Cuomo then dissolves the alcohol extract in an aqueous-alcoholic solution. JA1043 at Col.14, ll.13-14. However, the dissolving step does not make that solution an aqueous or aqueous-alcoholic ***extract*** of olives, but instead it is a aqueous-alcoholic ***solution*** made from an alcohol extraction from olives. *Id.* Thus, the District Court's misapprehension of the technology, led it to a scientifically untenable conclusion that Cuomo disclosed testing of an aqueous extract of olives when it, in fact, only disclosed testing an aqueous-alcoholic solution derived from an alcohol extract of olives.

Moreover, in its Motion for Summary Judgment, Pinnaclife submitted only attorney argument to support its arguments that Cuomo anticipates the '808 Patent. Pinnaclife failed to submit ***any*** evidence of how one of skill in the art interpreted the disclosures in Cuomo, and could not rebut the expert opinions of CreAgri's expert witness. In so doing, it failed to meet its burden of proving anticipation by clear and convincing evidence. *See Elcommerce.com, Inc. v. SAP AG*, No. 2011-1369, 2014 WL 685622, at *14 (Fed. Cir. Feb. 24, 2014)(holding district court erred in granting summary judgment based on only attorney argument and stating "[n]or can it be assumed that, without evidence, a general purpose judge could ascertain the position of persons of skill in the art…"); *see also Crown Packaging Tech., Inc. v. Rexam Beverage Can Co.*, 559 F.3d 1308, 1315 (Fed. Cir.

2009)(holding attorney argument insufficient to support summary judgment and rebuttal expert evidence created genuine issue of material fact). Therefore, the District Court did not have clear and convincing evidence to find anticipation, and granting summary judgment of invalidity was erroneous.

For these reasons, CreAgri presented sufficient evidence to create a genuine issue of material fact that precluded summary judgment. Therefore, this Court should reverse the District Court's finding of anticipation by Cuomo.

D. Pinnaclife Did Not Prove By Clear and Convincing Evidence That Romani Anticipates Claims 1, 2, 5, and 6 of the '808 Patent

The District Court erred in finding anticipation by Romani based on its erroneous claim construction of the term "aqueous extract of olives" to include aqueous-alcoholic extracts. There was no finding by the District Court that Romani disclosed pure aqueous extracts. Therefore, as discussed above, if the District Court's claim construction is reversed, then the finding of anticipation should also be reversed. Additionally, even with the District Court's incorrect claim construction, there are material issues of fact that preclude summary judgment. Like Cuomo, Romani does not disclose an aqueous extract of olives even under the District Court's incorrect claim construction of that term.

Romani started with the olive pulp, not the aqueous (waste water) extract, and began a complex processing step to obtain test material. JA2422-23 at ¶ 75. As CreAgri's expert, Dr. German, stated in his sworn declaration, Romani took

olive pulps frozen in liquid nitrogen, ground them, and used ethanol to extract the polyphenols. *Id.* Romani then concentrated the "raw ethanolic extracts" and rinsed with acid water to form an "aqueous solution." *Id*. This aqueous solution was "then extracted more times with *n*-hexane to completely remove lipophilic compounds, and the aqueous phase was concentrated." *Id*.

Thereafter, the solution is loaded on a Extrelut cartridge and eluted with three different non-aqueous solutions (1) n-hexane, (2) ethyl acetate (EtOAc), and (3) acid methanol. Romani at 965. As Dr. German pointed out, the polyphenols (hydroxytyrosol, oleuropein) are extracted in a non-aqueous solution of ethyl acetate and dried. JA2423 at ¶ 75. Dr. German explained that Romani describes an extract collected in ethyl acetate (EtOAc), which is "immiscible in water,"[5] and not an "aqueous" solution. JA2422 at ¶ 73. One skilled in the art would know that Romani does not disclose aqueous extracts of olives, because it discloses repeated manipulation and purification of the extract with non-water solvents. JA2422-23 at ¶¶ 73, 75; (*see* Figure 3 below). As demonstrated in Romani's figures 1 and 2, the tests for phenols were from the ethyl acetate (EtOAc) and acid methanol fractions from the cartridge, and were not from an aqueous extract – in fact they

[5] Dr. German explained, "[t]he history of applied chemistry is full of examples in which specific solvents are the entire basis of particular products and formulations. Referring to an ethyl acetate extract as identical to an 'aqueous extract' (from water) is simply not true." JA 2422 at ¶ 72.

were not even from the aqueous solution phase after the acid water rinse. JA982-83.

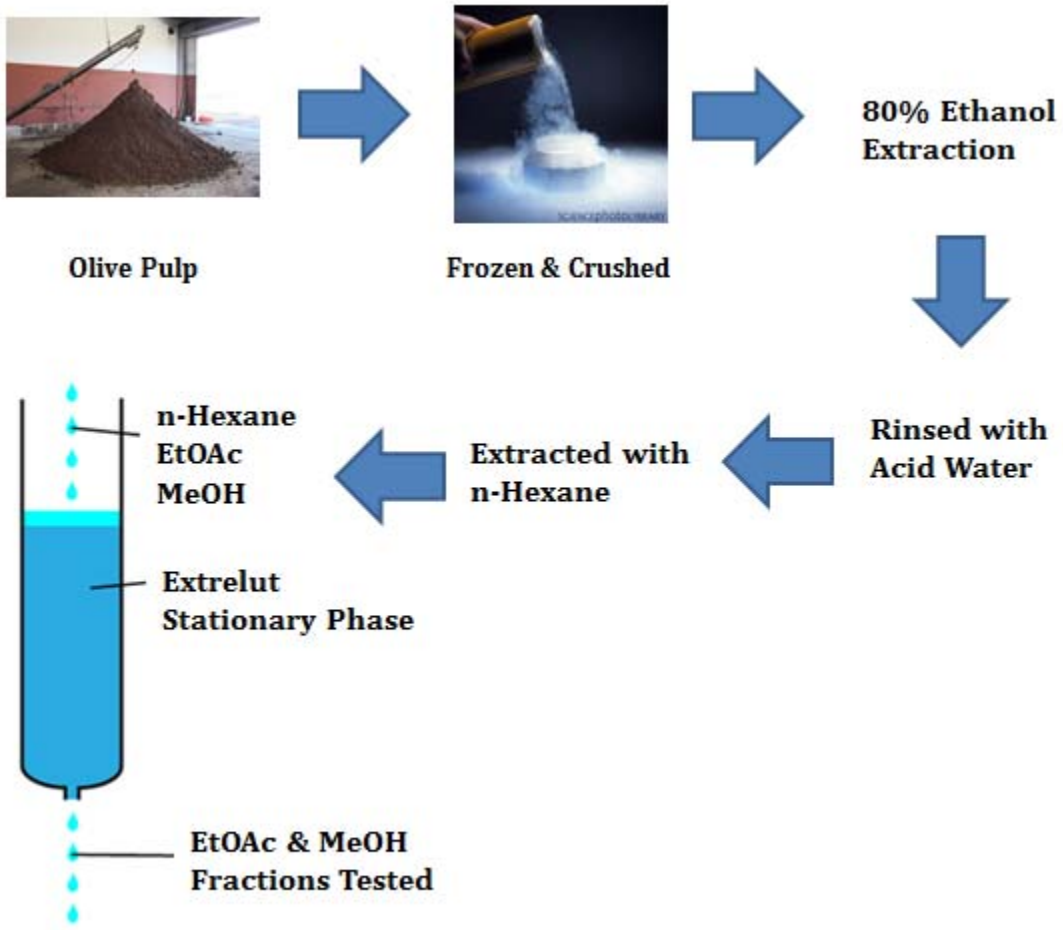

Figure 3: The Romani processing steps

The District Court erroneously concluded that the "aqueous solution" and "aqueous phase" were the claimed "aqueous extract of olives" in the '808 Patent. It stated: "[t]he premise of this procedure is that the intermediate steps in the measurement process (during which the authors obtain the aqueous extract of olives) do not alter the hydroxytyrosol, tyrosol, and oleuropein levels naturally

found in the Rossellino cultivar." JA16. It did not cite to any evidence in the record to support this assumption, particularly no evidence submitted from one of skill in the art. Rather, it substituted its lay opinion for that of one of skill in the art. Pinnaclife, itself, did not offer any evidence from its expert or any other person of skill in the art stating that the repeated manipulation and purification steps in Romani did not alter the weight ratios of the phenolic compounds.

However, CreAgri's expert specifically opined that the weight ratios obtained in Romani were not the same as what was in the intermediate "aqueous solution" or "aqueous phase," because they were obtained after repeated use of organic solvents, and after "concentrated" to a solid state. JA2422-23 at ¶¶ 74-75. In other words, the hydroxytyrosol, tyrosol, and oleuropein levels reported in Romani were from the ethyl acetate (EtOAc) and acid methanol fractions – not from an aqueous extract, the aqueous solution or any aqueous phase. JA2422 at ¶ 73. Because the rebuttal evidence submitted by CreAgri's expert establishes a genuine issue of material fact regarding anticipation by Romani, the District Court erred in granting summary judgment of invalidity.

Pinnaclife failed to prove, by clear and convincing evidence, that Romani anticipates the '808 Patent. Similar to Cuomo, Pinnaclife's evidence with respect to the disclosures in Romani were limited to attorney argument. Pinnaclife did not point to any opinions from one of skill in the art interpreting the disclosures in

Romani. Rather, its counsel simply argued that the term "aqueous solution" in Romani was the same as the "aqueous extract" claimed in the '808 Patent.

For these reasons, CreAgri presented sufficient evidence to create a genuine issue of material fact that precluded summary judgment. Therefore, this Court should reverse the District Court's finding of anticipation by Romani.

E. The District Court Erred in Finding the '599 Patent Invalid for Lack of Written Description

The District Court applied an overly stringent standard for written description by requiring actual medical proof of the claimed inventions within the speciifcation rather than just disclosure sufficient to one of skill in the art.[6] JA26 ("None of those references, however, demonstrate the *medical efficacy* of hydroxytyrosol, hydroxytyrosol together with oleuropein, or olive plant extract having a given ratio of hydroxtyrosol to oleuropein, for treating inflammation arising out of the numerous cases recited in the claims of the '599 Patent.") (emphasis added).

The District Court erroneously rewrote the claims of the '599 Patent to insert a "medically effective" limitation that simply does not exist in the claims as written. *See Resonate*, 338 F.3d at 1365 ("[c]ourts may not rewrite claim language based on

[6] The District Court's level of ordinary skill in the art was "someone with a bachelor's degree or higher in Food Science or related Biological fields related to diet and health and/or several years of experience in the life sciences research industry." JA20 n.12.

what has been omitted from a claim, and the district court's attempt to do so here was legal error"). Both independent claims of the '599 Patent (Claims 1 and 16) simply claim treatment of inflammatory conditions, rather than claiming that the treatments are necessarily "medically effective." Therefore, the Court's finding of invalidity was erroneous. As discussed below, CreAgri provided substantial written description to one of skill in the art to understand what was being claimed. For reasons discussed in detail below, the District Court's grant of summary judgment of invalidity should be reversed.

1. The Specification of the '599 Patent, Itself, Provided Detailed Information For One of Skill in the Art To Understand What Was Being Claimed

CreAgri provided substantial evidence of written description in its Opposition to Pinnaclife's Motion for Summary Judgment. Within the twenty-column specification of the '599 Patent, the patentee discussed how to practice the claimed methods using the claimed compositions of olive-extracted compounds. Specifically, the inventor disclosed how to prepare compounds for use with the claimed methods of treatment. *See, e.g.*, JA83-89 at Col.2, ll.33-51, Col.3, ll.16-20, Col.3, ll.41-45, Col.5, l.21-Col.7, l.49, Col.13, ll.21-26; *see also* JA2500-04 at 187:15-188:1, 190:19-192:2.

The specification also disclosed detailed examples of practicing the claimed methods. JA90-92 at Col.16, l.35-Col.19, l.24. The first three examples in the

specification discuss subjects who were suffering from an HIV-associated cognitive dysfunction (a neurological disorder) and had neuro inflammation treated with the claimed olive extracts. These examples specifically discuss neuropsychiatric testing and monitoring CSF isoprostane levels as set forth in Claim 1 of the '599 Patent. JA90-91 at Col.16, l.59, Col.17, ll.5-6, Col.17, ll.19-22, Col.17, ll.46-55; JA92 at Col.20, ll.3-5.

Initial results from the study were obtained as disclosed in the '599 Patent specification, and showed a statistically favorable change in 8-isoprostane levels in urine. JA91 at Col.18, ll.36-39. CreAgri's inventor testified that these initial results were understood by one of skill in the art to correlate to monitoring cerebral spinal fluid (CSF) ("central fluid") levels of isoprostanes in the claimed methods. JA2648 at 186:17-21 (inventor testifying that "with the knowledge we had at that time, you know, we had a clinical approach which made a lot of sense, to correlate isoprostane…you find in central fluid to the one you find in urine"). Pinnaclife presented no contrary opinion from one of skill in the art.

The District Court took issue with the fact that the study disclosed in the first three examples was only for a small sample size ("up to 32 subjects"). JA24. However, the specification makes clear that "the sample size is reasonable for a pilot safety and tolerability study." JA91 at Col.18, ll.10-11. Whether the study was intended to be of "statistical significance," as the District Court noted, is

irrelevant to adequate written description, as there was no evidence in the record that a larger sample size was necessary for one of skill in the art to understand what is being claimed. The District Court, in concluding there was a lack of written description, simply relied upon Pinnaclife's counsel's argument without any record evidence from one of skill in the art.

Example 4 in the '599 Patent also discusses protocols and *in vivo* studies implementing the claimed methods and monitoring markers or clinical symptoms such as the levels of C-reactive protein ("CRP") in the treatment of arthritis. JA91-92 at Col.18, l.40-Col.19, l.24. The District Court also found this example deficient because no final data was reported. JA24. However, to satisfy written description under the appropriate legal standard, there need only be sufficient disclosure to one of skill in the art describing what is actually claimed, without necessarily showing that it was, in fact, actually done or successful. *See, e.g. Falko-Gunter Falkner v. Inglis*, 448 F.3d 1357, 1366 (Fed. Cir. 2006)(holding actual reduction to practice not required for written description); *see also Union Oil Co. of Cal. v. Atlanta Richfield, Co.*, 208 F.3d 989, 997 (Fed. Cir. 2000)("[t]he written description requirement does not require the applicant to describe exactly the subject matter claimed, instead the description must clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed") (internal citations and quotation omitted).

In fact, CreAgri submitted evidence from one of skill in the art (Dr. Bruce German) showing that the disclosures in the '599 Patent were sufficient. JA2428 at ¶ 95 ("The patent discloses reasonable and appropriate biomarkers related to the complex and diverse processes of inflammation according to current scientific convention. One of skill in the art would readily apply the descriptions in the '599 Patent to the documentation of health consequences of consuming extracts of olives according to the patent describing their preparation. Therefore it is inherent in the description of the patent and the appropriate markers to be measured that these be applied to a susceptible population using markers that were well understood by persons of skill in the art."). Therefore, the District Court's finding of a lack of written description was erroneous.

Finally, the District Court erroneously dismissed parts of the '599 Patent specification as irrelevant simply because it discussed treatment of a "neurological disorder" associated with AIDS. JA21. However, the inventor explicitly discussed inflammation associated with the neurological disorder in these sections of the specification, and Claim 1 of the '599 Patent specifically identifies nuero inflammation as an inflammatory condition. JA86 at Col.8, ll.27-30 ("While some viral products are neurotoxic in brain cell cultures, it appears that *proinflammatory* molecules, secreted by or inducted by macrophages, are main effectors of ongoing brain injury") (emphasis added); JA87 at Col.9, ll.58-59 ("[t]he CSF typically has

an *inflammatory* pattern, and sometimes CMV can be cultured from the CSF") (emphasis added); JA88 at Col.11, ll.4-8 ("It is known that free radicals (oxidative stress) of different types are associated with a range of diseases…allergic/*inflammatory* conditions such as bronchial asthma and rheumatoid arthritis…") (emphasis added); JA88 at Col.11, ll.32-35 ("Different conditions such as *inflammations*, infections…give rise to oxidative stress which leads to the different conditions and diseases stated above") (emphasis added); JA88 at Col.11, ll.48-63 (discussing types of "neuropsychological testing" used in the claimed methods). Therefore, the District Court erred in ignoring the above sections, simply because they did not fall under the heading of "inflammation" in the specification. JA21. For such reason, the District Court's finding of a lack of written description was legal error, and should be reversed.

2. Prior Art and Prior Knowledge of One of Skill In Art Supported Written Description of the '599 Patent

The District Court also decisively erred in failing to give appropriate weight to the knowledge of one of skill in the art in its analysis of written description. The record evidence showed that one of skill in the art would understand "why" the inventor was in possession of the claimed invention by reading the specification in light of what was known in the prior art. As discussed above, CreAgri's expert opined that written description is sufficient to for one to understand the claimed inventions. JA2428 at ¶ 95.

Notably, the '599 Patent included four pages of prior art references relevant to the claimed methods. JA78-81; JA92 at Col.19, ll.25-31 ("all publications and patent applications mentioned in this specification are indicative of the level of skill of those skilled in the art to which the invention pertains. [They] are herein incorporated by reference…"). The District Court found that such references only "explor[ed] the possibility of the anti-inflammatory use of hydroxytyrosol and oleuropein…but not at the point of inherently appreciating the use of these substances to treat" the inflammatory conditions in the claims of the '599 Patent. JA27-28. However, as discussed below, the prior art disclosures were sufficient for one of skill in the art to conclude the inventor was in possession of the claimed methods.

Five prior art references cited by example in CreAgri's opposition brief were highlighted for the District Court. First, the Fehri reference cited in the '599 Patent discussed the anti-inflammatory effect of aqueous dried leaf extract "containing 3.2% of oleuropein" on mice. JA2702-09 at JA2702. Fehri stated that "Olea europaea extract exerted an anti-inflammatory effect on carrageenin induced oedema (Figure 7b)." JA2706. It also stated that "One important result from the present experiment was that the anti-inflammatory effect mediated by the extract was observed during longer period in comparison with aspirin" and "pronounced anti-inflammatory and significant anti-ulceric effects were also recorded." JA2709.

While the article stated that "[t]hese demonstrated properties could be investigated in therapeutics," it never indicated that one of skill in the art had an expectation that the olive extract had no "therapeutic use" as the District Court concluded. *Id.* Rather, the article confirmed, based on the mice data, that the olive leaf extract did have anti-inflammatory properties which could benefit those suffering from inflammation.

Second, the Ragione reference stated: "The ability of DPE [hydroxytyrosol] to induce apoptosis in proliferating and resting normal peripheral lymphocytes represents a very promising finding. This effect might be important in explaining the molecular bases of the observed olive oil beneficial activities on human health, and particularly in the prevention of colon cancer. Indeed, it is well-established that inflammatory processes are involved in all steps of cancer transformation … Indeed, the down-regulation of lymphocyte proliferation….might be extremely useful in treating chronic inflammatory bowel pathologies…" JA2715-21 at JA2720. The District Court stated because two colon cell lines were resistant to the capability of DPE (hydroxytyrosol), the article was unable to draw a conclusion about the general anti-inflammatory effects of hydroxytyrosol. JA27. However, the District Court had no evidence that one of skill in the art would find the aberrant cell lines to affect the reasonable expection that the hydroxytyrosol had anti-inflammatory benefits.

Third, the Visioli reference showed data where the OMWW (olive mill waste water) extracts protected against damage "at the site of inflammation." JA945-49 at JA949. It also discussed "the potent inhibition of…stimulated production of LTB_4…suggest[ing] that OMWW extracts exert biological effects beyond their antioxidant properties." *Id.* As discussed below, LTB_4 is a pro-inflammatory molecule known to one of skill in the art. *See infra* at 55. The Kohyama and Petroni references also showed that the administration of hydroxytyrosol have the potential to reduce inflammation, as Pinnaclife conceded. JA859; JA1049-52; JA1054-63.

The District Court took exception with and discounted these studies because they were done *in vitro*, and not *in vivo* in human trials. JA27. The *in vivo* testing, however, should not have been dispositive of a lack of written description as this Court has determined that human testing is not required for patentability. *See In re '318 Patent Infringement Litig.*, 583 F.3d 1317, 1324 (Fed. Cir. 2009)("human trials are not required for a therapeutic invention to be patentable").

Numerous other references in the '599 Patent also discuss the beneficial properties of olive extracts used in the claimed methods. JA79 at 2 (Visioli F. et al., "Olive oils rich in natural catecholic phenols decrease isoprostane excretion in humans," *Biochem Biophys Res Commun* 278(3): 797-799, 2000; Visioli, "'Waste waters' from olive oil production are rich in natural antioxidants," Experientia, vol.

51, No. 1, pp. P32-P34, 1995, Abstract Only, Visioli et al., "Olive phenol hydroxytyrosol prevents passive smoking-induced oxidative stress," Circulation, vol. 102, No. 18, pp. 2169-2171 (2000)).

Based on the record evidence, it was error for the District Court to find that these references did not disclose sufficient relevant information for the '599 Patent to satisfy the written description requirement. In essence, the only way it appears that the District Court would have found compliance with the written description requirement was if the prior art disclosed exactly what was claimed in the '599 Patent. Under the District Court's standard, the written description requirement could only be satisfied if the prior art anticipated or made obvious the claimed inventions. Such a standard runs contrary to the purpose of filing a patent, *i.e*. the patentee is seeking to disclose its novel inventions to the public rather than simply regurgitate what is already known. For these reasons, the District Court's Order should be reversed.

The District Court also erred in placing too much weight on an isolated statement of CreAgri's inventor who testified at his deposition that patents, generally, could be "prophetic." JA909 at 174:12. Dr. Crea, in fact, testified that he "anticipate[d]" the claimed methods were effective at the time of the '599 Patent application. *Id.* at 174:16-19. Dr. Crea's testimony does not show that the claimed inventions were not sufficiently disclosed to one of skill in the art.

Therefore, the inventor's isolated testimony that Pinnaclife pointed to, without more, did not establish a lack of written description. For this reason, it was erroneous for the District Court to grant summary judgment of invalidity.

3. The District Court's Preconceived View of Written Description Colored Its Factual Analysis in a Bad Light

The District Court erred by starting its analysis with the faulty premise that "patents in [the field of chemical arts]—including patents directed to treating inflammation—are *often found* to lack a sufficient written description." JA19 (emphasis added). In its Order, it cited to a single case in support of this view, *Univ. of Rochester v. G.D. Searle & Co.*, 358 F.3d 916 (Fed. Cir. 2004). However, this Court has never held either in the *Univ. of Rochester* case nor in any other case that patents in the "chemical arts" are "often found" to lack a sufficient written description. Rather, this Court has held "[i]n written description cases, the primary consideration is *factual* and depends on the nature of the invention and the amount of knowledge imparted to those skilled in the art by the disclosure." *Union Oil Co. of Cal.*, 208 F.3d at 996 (citations omitted).

The single case cited by the District Court, *Univ. of Rochester*, has facts that are starkly different from this case. In *Univ. of Rochester*, there was a lack of written description because there was no disclosure of any compounds that could be used in the claimed methods. 358 F.3d at 920, 922. As this Court noted in that case, "[w]ithout such a compound, it is impossible to practice the claimed method

of treatment." *Id.* at 926. In this case, the '599 Patent discloses numerous examples of "treatment agents" and "substantially purified" phenolic compounds that are used in the claimed methods, including how to create them using methods known to those of skill in the art and disclosed in other patents. *See, e.g.*, JA83 at Col.2, ll.33-51; JA84 at Col.3, ll.16-20, Col.3, ll.41-45; JA85-86 at Col.5, l.21-Col.7, l.49; JA89 at Col.13, ll.21-26. Pinnaclife's expert, in fact, acknowledged at his deposition that the specification discloses a "reproducible" method to make the claimed olive plant extract. JA2500-04 at 187:15-188:25; 190:19-192:2. Therefore, the Court erred in starting with a faulty preconceived view of written description, and its Order should be reversed.

F. Pinnaclife Failed to Prove Lack of Enablement and Utility of the '599 Patent By Clear and Convincing Evidence

The District Court erred in finding a lack of enablement and utility for the claimed methods of the '599 Patent. Similar to its application of an erroneous written description standard, it improperly heightened the standard of proving enablement and utility as requiring one to prove medical efficacy of the claimed methods of treatment and disclose FDA clinical trials, rather than simply teaching *one of ordinary skill in the art* of how to make and use of the invention. This Court held in *In re '318 Patent Infringement Litig.*:

> Typically, patent applications claiming new methods of treatment are supported by test results. But it is clear that testing need not be conducted by the inventor. In addition,

> human trials are not required for a therapeutic invention to be patentable. Our predecessor court, the United States Court of Customs and Patent Appeals, held in *In re Krimmel* that patent applications need not 'prove that compounds or other materials which [the applicant] is claiming, and which [the applicant] has stated are useful for pharmaceutical applications are safe, effective, and reliable for use in humans.

583 F.3d at 1324 (citations omitted). As this Court set forth in *In re Brana*:

> FDA approval, however, it not a prerequisite for finding a compound useful within the meaning of the patent laws. [] Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans. Were we to require Phase II [human clinical] testing in order to prove utility, the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many crucial areas such as the treatment of cancer.

51 F.3d 1560, 1568 (Fed. Cir. 1995)(citation omitted). The PTO's Manual of Patent Examining Procedure (MPEP) also states, "If reasonably correlated to the particular therapeutic or pharmacological utility, data generated using *in vitro* assays, or from testing in an animal model or a combination thereof almost invariably will be sufficient to establish therapeutic or pharmacological utility for a compound, composition or process"). MPEP § 2107.03.

Furthermore, the District Court erred in placing the burden on CreAgri to prove enablement and utility given the claimed inventions were not so "inherently

unbelievable." *See In re Brana*, 51 F.3d at 1566 ("[o]nly after the PTO provides evidence showing that one would reasonably doubt the asserted utility does the burden shift to the applicant to provide rebuttal evidence sufficient to convince such a person of the invention's asserted utility."). As this Court held in *In re Brana*:

> [A] specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must* be taken as in compliance with the enabling requirement of the first paragraph of § 112 *unless* there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.

51 F.3d at 1566 (quoting *In re Marzocchi*, 438 F.2d 220, 223 (CCPA 1971)). For example, an invention that relates to controlling an aging process may provide "reason to doubt" the utility because it would suggest an "inherently unbelievable undertaking or involve implausible scientific principles." *In re Cortright*, 165 F.3d 1353, 1357 (Fed. Cir. 1999)(internal quotations and citations omitted).

As discussed above, the claimed methods of treating inflammation with extracted compounds from olives were not so "inherently unbelievable" or "implausible" to one of skill in the art such that there was credible reason to doubt the utility of the claimed methods. The District Court improperly placed the burden on CreAgri to prove enablement and utility of the claimed inventions, when

the claimed methods are presumptively enabled and useful. Therefore, its Order should be reversed.

1. Pinnaclife Failed To Show It Would Require Undue Experimentation To Practice the Claimed Inventions of the '599 Patent

The burden of proof remained on Pinnaclife alone to prove a lack of enablement, and to show that undue experimentation would be required to practice the claimed methods of the '599 Patent. *See Cephalon*, 707 F.3d at 1337-40 (reversing finding of lack of enablement when defendant failed to carry its burden of showing clear and convincing evidence that undue experimentation was required).

In its Opening and Reply briefs supporting its Motion for Summary Judgment, Pinnaclife never once addressed the amount of experimentation that would be required to practice the claimed methods of the '599 Patent. It did not offer any testimony or documentary evidence from one of skill in the art opining on the degree of experimentation necessary to practice the claimed methods. *See id.* at 1338 ("[u]nsubstantiated statements indicating that experimentation would be 'difficult' and 'complicated' are not sufficient"). Notably, its expert offered no opinion at all whether the '599 Patent lacked utility under Section 101.

Rather, Pinnaclife simply made attorney argument that the disclosures in the '599 Patent specification were insufficient to be enabling, and attempted to shift

the burden on CreAgri to prove the patents were enabled. This was improper. *See id.* at 1337-40 (reversing finding of lack of enablement when defendant failed to carry its burden of showing clear and convincing evidence that undue experimentation was required).

Even if CreAgri had any burden to show enablement, it more than satisfied this burden by submitting evidence in the form of a sworn declaration of its technical expert, Dr. Bruce German, that one of skill in the art would have read the disclosure in the '599 Patent and understood how to use the claimed methods. JA2380 (JA2428 at ¶ 95: CreAgri's expert opining that the '599 Patent specification discloses sufficient information combined with documentation of health consequences of consuming extracts of olives for one of skill in the art to use the claimed inventions).

CreAgri's expert, Dr. German, is exceptionally qualified to provide his opinions as one of skill in the art. *See* JA2407-08, 2432-75 at ¶¶ 1-5, Ex. A. Pinnaclife's only response to CreAgri's evidence that one of skill in the art could practice the invention with routine experimentation was to state in its reply brief, that: "Even if there were evidence that one skilled in the art could reproduce the olive plant extract, that does not necessarily mean that one skilled in the art could treat the conditions claimed in the patent." JA2800-01. It did not cite any record testimony from one of skill in the art to support this conclusion. *See Moba, B.V. v.*

Diamond Automation, Inc., 325 F.3d 1306, 1321 (Fed. Cir. 2003)(finding that there was no record evidence recounting the amount of experimentation one of skill in the art would require to develop the claimed invention based on the patent's disclosure). In fact, Pinnaclife's expert testified that the claimed methods are so "easy." JA2500-01 at 187:25-188:25. Because Pinnaclife never set forth any proof that any experimentation would be "undue," the District Court's Order was erroneous and should be reversed.

2. The District Court Erred In Finding Pinnaclife's Expert's Unsworn Statements "Uncontroverted"

Moreover, as support for its Order, the District Court relied on unsworn statements of Pinnaclife's expert that there was no anti-inflammatory properties of hydroxytyrosol and oleuropein prior to the '599 Patent. JA30. Pinnaclife did not even submit these statements as evidence in support of its Motion for Summary Judgment. Even if the District Court could have considered evidence that was not argued by either party, CreAgri's expert disputed those statements and stated, "Dr. Visioli's own publications assert that antioxidant activity was related to anti-inflammatory activity in 2001 and 2002 so it is difficult to interpret the logic of his arguments." JA2418 at ¶ 55.

Specifically, Dr. German cited to Visioli's publications, "Antiatherogenic Components of Olive Oil" and "Antioxidant and Other Biological Activities of Phenols from Olives and Olive Oil" that showed antioxidant activity of olive

extracts as related to anti-inflammatory activity. *Id.* The District Court held that Dr. German's opinions and cited articles were insufficient to "create an issue of fact as to whether a person of ordinary skill in the art would accept the claimed therapeutic effect of olive-derived phenolic compounds in humans or other animals," but did not rely on any evidence from one of skill in the art in support of this statement. When there is a disagreement between experts, it is improper to grant summary judgment. *See Edwards Sys. Tech., Inc. v. Digital Control Sys., Inc.*, 99 Fed. Appx. 911, 922 (Fed. Cir. 2004)(holding "conflicting evidence demonstrates a classic battle of the experts….and thus creates a genuine issue of material fact").

In fact, both articles explicitly mention the numerous therapeutic benefits and anti-inflammatory properties of hydroxytyrosol and oleuropein (olive phenolic compounds) from *in vitro* and *in vivo* studies. *See* JA3328-31 at JA3328 ("phenolic compounds, notably hydroxytyrosol and oleuropein"); JA3332-42 (same). The two articles, "Antiatherogenic Components of Olive Oil" and "Antioxidant and Other Biological activities of Phenols from Olives and Olive Oil" are very similar, with nearly identical text. Both articles concern reduction of the risk of coronary heart disease (CHD) with the intake of olive phenolic compounds, and the article, "Antioxidant and Other Biological Activities of Phenols from

Olives and Olive Oil," also discusses reducing the risk of cancer. Both articles state:

> "a scavenging effect of HT [hydroxytyrosol] and OE [oleuropein] was demonstrated with respect to hypochlorous acid, a potent oxidant produced in vivo at the site of *inflammation*…HT [hydroxytyrosol] has been tested for activities in addition to its antioxidant properties, such as the *in vitro* effects on platelet function, where the compound was *proven to inhibit*…the production of the pro-inflammatory molecule leukotrienes by activated human leukocytes….The potent (effective concentration $_{50s}$ in the 10^{-5} M range) inhibitory effect of HT [hydroxytyrosol] toward all these parameters [discloses or reveals] unpredicted biologic activities of olive oil phenolics that go beyond their antioxidant properties.

JA3329 (emphasis added); JA3336-37 (emphasis added). Both also disclose a table ("Table 1") listing a number of "biologic activities of olive oil phenolics" including "Reduced thromboxane 2 (TXB_2) and leukotriene B4 (LTB_4) production by activated leukocytes," related to the reduction of inflammation as shown in the excerpt above. JA3330; JA3338.

The disclosures in these articles show that persons of ordinary skill in the art, including the author Pinnaclife's own expert, understood hydroxytyrosol and oleuropein, to have therapeutic properties, including the inhibition of inflammation. However, the District Court applied an unnecessarily heightened standard that a person of skill in the art would accept "without question" that the claimed compounds had therapeutic effects. *See In re '318 Patent Infringement Litig.*, 583

F.3d at 1324 (holding human trials are not required for a therapeutic invention to be patentable). Based on the explicit disclosures in the prior art, there was clearly more than just a "hope" that these compounds had therapeutic benefits to persons of skill in the art. In fact, the prior articles of Pinnaclife's expert shows that that persons of skill in the art had begun to recognize the therapeutic benefits of phenols used in the claimed methods of the '599 Patent, prior to the time the '599 Patent application was filed. Therefore, this Court should reverse the District Court's Order.

3. The District Court Erred In Dismissing Peer-Reviewed Publications of The Inventor

At least two peer-reviewed articles published after the filing date of the '599 Patent confirmed the utility of the studies disclosed in the examples of the specification. *See Eli Lilly & Co. v. Actavis Elizabeth LLC*, 435 Fed. Appx. 917, 925 (Fed. Cir. 2011)("[w]hen priority is not at issue, generally the applicant may provide data obtained either before or after the patent application was filed [to demonstrate utility]").

Both articles were authored by the inventor of the '599 Patent. The first article, "Hydrolyzed Olive Vegetation Water in Mice Has Anti-Inflammatory Activity," was published in 2005 and showed the practical efficacy of the claimed methods described in the mouse study of Example 4 of the specification. *See* JA2750-54; JA92 at Col.19, ll.7-18 (discussing mouse model evaluating reduction

of levels of TNF-α). Specifically, the article stated that "OVW significantly decreased production of TNF-α after LPS treatment in THP-1 cells, a model of joint inflammation. TNF-α is the primary cytokine induced in this system and the cytokine responsible for the perpetuation of the inflammatory response in monocytes." JA2753.

While the article stated that "pure HT" (pure hydroxytyrosol) was ineffective in certain anti-inflammatory cell models (as the District Court noted), it also concluded that OVW (which had concentrations of hydroxytyrosol and oleuropein of 50 and 11%) had anti-inflammatory effect. JA2751-52. This ratio of hydroxytyrosol and oleuropein (4.5 to 1) falls directly within the scope of Claim 1 of the '599 Patent (claiming ratio of between about 1:1 and about 200:1).

The second article, "Olive extract supplement decreases pain and improves daily activities in adults with osteoarthritis and decreases plasma homocysteine in those with rheumatoid arthritis," authored by the inventor and published in 2007, also provided significant evidence of the practical utility of the claimed methods. JA2756-63. The article verified the success of the arthritis study set forth in Example 4. JA91 at Col.18, ll.44-50 ("Test a group of individuals with Rheumatoid Arthritis and a group with Osteoarthritis with the stress reactivity protocol, before and after 4 weeks of active agent (20 mg total phenols) supplementation…"). The article specifically showed, as the District Court noted,

a "statistically significant reduction in several of the subjects' inflammation symptoms over the placebo group." JA34.

The District Court ultimately did not find the article supported utility of the claimed inventions because it "did not mention hydroxytyrosol or oleuropein," and only referred to treatment of arthritis, not the other inflammatory conditions in the claims. Both of these reasons were erroneous in light of the disclosures in the article.

First, the article discussed the use of "OVW" to treat rheumatoid arthritis and cited to "references 13 and 14" of the article. "Reference 14" is the article discussed above ("Hydrolyzed olive vegetation water in mice has anti-inflammatory activity"), also authored by the inventor. As discussed above, Reference 14 shows the "OVW" comprises a percentage of hydroxytyrosol and oleuropein that falls within Claim 1 of the '599 Patent. Therefore, it would be apparent to one of skill in the art reading the article that "OVW" included hydroxytyrosol and oleuropein, even if not explicitly mentioned.

Second, the article clearly establishes that the OVW decreased pain and inflammation associated with arthritis by way of analysis of biomarkers, including C-Reactive protein levels (CRP). JA2759 ("Plasma levels of CRP were measured….Patient changes over time were compared using analysis…for biochemical markers (homocysteine and CRP)"); JA2760 ("After 8 weeks of

treatment, there was a significant improvement (> 20%) in OVW supplement-treated OA patients vs placebo-treated OA patients (Table 3)…Significant changes in CRP from V1 to V5 were detected"); JA2761 ("In the current study, an olive extract supplement given to patients with OA and RA decreased pain and inflammation associated with OA, improved quality of life, and decreased biochemical markers of systemic inflammation in patients with RA"); JA2762 ("C-reactive protein was significantly decreased by OVW supplement and this effect was most notable in patients with RA. C-reactive protein has long been a measure of inflammation in patients with RA, and studies have shown a correlation in CRP levels to disease activity… Unlike current medications that have been found to place users at risk for CVD, OVW acts both as an anti-inflammatory and cardioprotective agent.").

The fact that the other claimed inflammatory conditions were not explicitly stated in the article does not render the claims invalid for lack of enablement. One of skill in the art would understand that the claimed olive extracts could be used to treat other inflammatory conditions based on what was disclosed in the articles as well as the prior art references showing the anti-inflammatory benefits of olive extracts containing hydroxytrosol and oleuropein. *See supra* at 42-46.

CreAgri's expert expressly opined that one of skill in the art would understand how to analyze biomarkers of inflammation based on what was known

in the field: "[i]n ostensibly every publication on CRP the average levels within a normal unaffected population are included in published datasets…the literature then and now is replete with example datasets of normal ranges of CRP as a biomarker of inflammation." *See* JA2429 at ¶ 97; *see also* JA2598-601 at 87:6-90:11. He also testified that he had "overseen studies, reviewed papers, and examined literature on this issue," and "C-reactive protein as a marker of heightened inflammation state has been recognized in scientific literature for over a decade." JA2597 at 86:2-19. Thus, it would have been apparent for one of skill in the art to conclude that C-reactive protein is a general marker for inflammation, and not just a marker for inflammation associated with rheumatoid arthritis but other inflammatory conditions, including coronary inflammation and the other types of inflammation in the claims of the '599 Patent.

4. The District Court Erred in Analogizing The Facts of This Case To Those in *In re '318 Patent Infringement Litig.*

Furthermore, the District Court, in its Order, erroneously compared this case to *In re '318 Patent Infringement Litig.*, and held that "analytic reasoning" outside of actual testing was insufficient to establish utility in this case. In that case, the patentee did not contend that the prior art testing or any other data existed to support utility of the claimed inventions. 583 F.3d at 1325. However, in this case, as discussed above, the studies disclosed in the specification of the '599 Patent, confirmed in post-filing publications, showed the practical utility of the claimed

inventions. And, unlike the case *In re '318 Patent Infringement Litig.*, CreAgri submitted the opinions of its expert that one of skill in the art would find utility from the disclosures of the specification. *See supra* at 38-46.

The District Court also distinguished the holdings of *Brana* and *Actavis,* but those cases are, in fact, similar to the case at bar. In *Brana*, the patented chemical compounds were found to meet the utility requirement despite the fact that only preclinical animal tests were disclosed in the patent. 51 F.3d at 1567. Similarly, in this case, animal tests and other studies showed the practical utility of the claimed methods. *See supra* at 38-46, 58-60. As in *Brana*, the District Court "confuses the requirements under the law for obtaining a patent with the requirements for obtaining government approval to market a particular drug for human consumption." 51 F.3d at 1567 (citing *Scott v. Finney*, 34 F.3d 1058, 1063 (Fed. Cir. 1994)("[t]esting for the full safety and effectiveness of a prosthetic device is more properly left to the Food and Drug Administration (FDA). Title 35 does not demand that such human testing occur within the confines of Patent and Trademark Office (PTO) proceedings"). In *Brana*, this Court held that "statistically significant tests with standard experimental animals is sufficient to establish utility." 51 F.3d at 1567. As discussed above, the statistically significant mice tests for the '599 Patent showed the utility of the claimed methods. *See supra* at 56-60.

The District Court also tried to distinguish *Actavis* by finding there was no "suggestion that the FDA has approved human trials of the claimed or similar substances" in this case as in *Actavis.* However, in *Actavis*, it was undisputed that persons of skill in the field of the claimed treatments of ADHD "would require actual human tests to verify the[ir] effectiveness." 435 Fed. Appx. at 923-24. The claimed methods of treatment were subject to the FDA guidelines, and this Court found the initiated human clinical trials as persuasive evidence of utility, despite them not being disclosed at the time the patent application was filed. *Id.* at 924. As discussed above, there is no requirement for FDA trials in order for enablement to be satisfied, and the experts in this case disagreed whether human trials were required to show the efficacy of the claimed method. As in *Actavis*, there is no evidence that the disclosure in the '599 Patent is "on its face, contrary to generally accepted scientific principles." *Id.* at 925-26 (citing *In re Marzocchi*, 439 F.2d at 223). CreAgri submitted evidence that one of skill in the art would be able to understand and practice the claimed methods according to the disclosure in the specification. *See supra* at 38-60.

Therefore, for the reasons set forth above, the record evidence established genuine issues of material fact precluding summary judgment. Accordingly, the Court's Order should be reversed.

CONCLUSION AND STATEMENT OF RELIEF SOUGHT

Based on the arguments herein, the District Court's final judgment of invalidity of the '808 and '599 Patents should be reversed.

Dated: March 10, 2014

Respectfully submitted,

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UNITED STATES DISTRICT COURT

NORTHERN DISTRICT OF CALIFORNIA

SAN JOSE DIVISION

CREAGRI, INC., a California corporation, Plaintiff, v. PINNACLIFE INC., a Nevada corporation, Defendant.	Case No.: 5:11-CV-06635-LHK JUDGMENT

The Court granted Pinnaclife's Motion for Summary Judgment of Invalidity. *See* ECF No. 177. Accordingly, judgment is entered in favor of Pinnaclife.

IT IS SO ORDERED.

Dated: January 3, 2014

Lucy H. Koh

LUCY H. KOH
United States District Judge

UNITED STATES DISTRICT COURT

NORTHERN DISTRICT OF CALIFORNIA

SAN JOSE DIVISION

CREAGRI, INC., a California Corporation, Plaintiff, v. PINNACLIFE, INC., a Nevada Corporation, Defendant.	Case No.: 11-CV-6635-LHK ORDER GRANTING DEFENDANT'S MOTION FOR SUMMARY JUDGMENT OF INVALIDITY

Plaintiff CreAgri, Inc. ("CreAgri") brings this action against Defendant Pinnaclife, Inc. ("Pinnaclife") for infringement of U.S. Patent No. 6,416,808 (filed Aug. 31, 2001) ("the '808 Patent") and U.S. Patent No. 8,216,599 (filed Feb. 13, 2003) ("the '599 Patent"). *See* Second. Am. Compl., ECF No. 50. Before the Court are Pinnaclife's Motions for Summary Judgment of Invalidity, ECF No. 103 ("Def. MSJ"), and Noninfringement,[1] and CreAgri's Motion for Summary Judgment of Infringement, ECF. No. 106 ("Pl. MSJ"). Having reviewed the parties' submissions, the record in this case, and the relevant law, the Court GRANTS Pinnaclife's Motion for Summary Judgment of Invalidity. The Court concludes that all claims of the '808 Patent are invalid as anticipated under 35 U.S.C. § 102 and that all claims of the '599 Patent are invalid for failure to

[1] Although Pinnaclife moved for summary judgment of invalidity only and CreAgri moved for summary judgment of infringement only, Pinnaclife, *see* ECF No. 155 at 4, moved for summary judgment of noninfringement as part of its opposition to CreAgri's motion for summary judgment, *see* ECF No. 113-1 ("Pl. Opp.").

meet the written description, enablement, and utility requirements of 35 U.S.C. §§ 101 and 112(a). Because the Court concludes that all claims of the patents-in-suit are invalid, the Court does not reach the issues raised in CreAgri's Motion for Summary Judgment of Infringement or Pinnaclife's Motion for Summary Judgment of Noninfringement.

I. BACKGROUND

A. Factual Background

CreAgri and Pinnaclife both sell products, including dietary supplements, containing olive-derived phenolic compounds intended to promote health. Pl. Opp. at 2.[2] Olives naturally contain the phenolic compounds oleuropein, hydroxytyrosol, and tyrosol. '808 Patent 2:9–30. Olive oil is a principal fat component of the Mediterranean diet, which has been linked to a lower incidence of certain ailments, such as coronary heart disease and some cancers. *Id.* 2:9–14. Massive amounts of "waste water" or "vegetation water" are produced as a byproduct of olive oil production. Discarding this water creates a significant economic burden for olive oil mills. *See* Francesco Visioli, et al., 47 *Antioxidant and Other Biological Activities of Olive Mill Waste Waters*, J. Agric. Food Chem., 3397–3401 (1999), *available at* Marshall Decl. Ex. D, ECF No. 103-2. Because of the known health benefits of olives and olive extracts, efforts have been made to leverage olive mill vegetation water for therapeutic uses, rather than simply discarding it as waste. CreAgri has secured, and now asserts, two patents over certain compositions of phenols derived from this waste water and uses thereof. '808 Patent; '599 Patent.

The '808 Patent, entitled "Method of Obtaining a Hydroxytyrosol-Rich Composition from Vegetation Water," claims, despite its title, *compositions* of olive-derived dietary supplements containing hydroxytyrosol and oleuropein or hydroxytyrosol and tyrosol at certain weight ratios. *See* '808 Patent at 3:43–51. The '808 Patent contains two independent claims and four dependent claims, all of which CreAgri asserts in this case. Independent claim 1 recites a range of hydroxytyrosol-to-oleoeuropein weight ratios and reads as follows:

> A dietary supplement comprising an aqueous extract of olives containing a weight ratio of hydroxytyrosol to oleoeuropein of between about 5:1 and about 200:1.

[2] Phenolic compounds are compounds with one or more phenyl ($-C_6H_5OH$) groups. Def. MSJ at 2. A compound with more than one phenyl group is a polyphenol.

Claims 2 through 4 depend from claim 1. Claim 2 recites a narrower range of hydroxytyrosol-to-oleoeuropein weight ratios. Claim 3 recites a dried supplement in powder form, and claim 4 recites an extract "in the form of a tablet, capsule, pill, or confection food additive." Independent claim 5 is similar to claim 1 except that it recites a range of hydroxytyrosol-to-tyrosol weight ratios:

> A dietary supplement comprising an aqueous extract of olives containing a weight ratio of hydroxytyrosol to tyrosol of between about 3:1 and about 50:1.

Dependent claim 6 recites a narrower range of hydroxytyrosol-to-tyrosol weight ratios. CreAgri filed the '808 Patent on August 31, 2001, and the Patent issued on July 9, 2002. *Id.*

The '599 Patent, entitled "Method for Treatment of Inflammation," relates to using olive plant extracts to "treat[] AIDS-associated neurological disorders, inflammation and inflammation-associated disorders." '599 Patent 1:10–14 ("Field of the Invention"). The claims recite methods for treating specified inflammatory conditions with various mixtures of hydroxytyrosol or hydroxytyrosol and oleuropein. *See* '599 Patent. The '599 Patent contains two independent claims and fourteen dependent claims. The first independent claim, claim 1, reads as follows:

> A method of treating a subject having an inflammatory condition characterized by a detectable clinical symptom or change in a level of a biochemical marker with respect to the normal range of the marker, the method comprising:
>
> administering to the subject a dose corresponding to between about 0.1 mg/kg body weight and 2000 mg/kg body weight daily of a first treatment agent comprised of an olive plant extract having a weight ratio of hydroxytyrosol to oleuropein of between about 1:1 and about 200:1; and
>
> continuing said administration until there is observed a return of the marker level to the normal range or a desired change in the clinical symptom,
>
> where the marker or the clinical symptom is selected from the group consisting of
>
> (i) elevated levels of C-reactive protein in the case of coronary inflammation;
>
> (ii) respiratory distress in the case of bronchial inflammation; and
>
> (iii) elevated CSF levels of isoprostanes or clinical symptoms determined from neuropsychological testing in the case of neuro inflammation.

All fourteen of the dependent claims depend from claim 1. The other independent claim, claim 16, uses a slightly different therapy—substantially purified hydroxytyrosol and oleuropein—to treat a broader set of conditions:

> A method of treating an inflammatory condition in a subject in need of such treatment, comprising administering to said subject a dosage amount corresponding to between about 0.1 mg/kg body weight and 2000 mg/kg body weight daily of substantially purified hydroxytyrosol or a substantially purified mixture of hydroxytyrosol and oleuropein, wherein said inflammatory condition is in response to a condition selected from the group

consisting of: delayed type hypersensitivity reaction, psoriasis, an autoimmune disease, organ transplant, pain, fever, and tissue graft rejection.

CreAgri filed the '599 Patent on February 13, 2003, and, following a long prosecution history, the Patent issued on July 10, 2012. '599 Patent.

B. Procedural Background

CreAgri filed its Complaint on December 23, 2011, alleging that Pinnaclife's olive-derived supplements infringe the '808 Patent. ECF No. 1. Following a first amendment and a successful Motion to Dismiss some of CreAgri's claims, *see* ECF Nos. 27, 46, CreAgri filed its operative complaint on January 1, 2013, alleging infringements of both the '808 and '599 Patents. *See* ECF No. 50. In its answer, Pinnaclife included counterclaims seeking declaratory judgments of invalidity and noninfringement of the '808 and '599 Patents, as well as a declaratory judgment that the '808 Patent was unenforceable due to inequitable conduct. *See* ECF No. 55. The Court issued an order construing the disputed claims of the Patents on April 16, 2013. ECF No. 67 ("Claim Construction Order"). Pinnaclife now moves for summary judgment on invalidity and noninfringement and CreAgri moves for summary judgment of infringement.

II. LEGAL STANDARD

A. Summary Judgment

Summary judgment is appropriate if, viewing the evidence and drawing all reasonable inferences in the light most favorable to the nonmoving party, there are no genuine disputed issues of material fact, and the movant is entitled to judgment as a matter of law. Fed. R. Civ. P. 56(a); *Celotex Corp. v. Catrett*, 477 U.S. 317, 322 (1986). At the summary judgment stage, the Court "does not assess credibility or weigh the evidence, but simply determines whether there is a genuine factual issue for trial." *House v. Bell*, 547 U.S. 518, 559–60 (2006). A fact is "material" if it "might affect the outcome of the suit under the governing law," and a dispute as to a material fact is "genuine" if there is sufficient evidence for a reasonable trier of fact to decide in favor of the nonmoving party. *Anderson v. Liberty Lobby, Inc.*, 477 U.S. 242, 248 (1986). Mere conclusory, speculative testimony in affidavits and moving papers is insufficient to raise genuine issues of fact and defeat summary judgment. *See Thornhill Publ'g Co. v. GTE Corp.*, 594 F.2d 730, 738 (9th Cir. 1979).

The moving party bears the initial burden of identifying those portions of the pleadings, discovery, and affidavits that demonstrate the absence of a genuine issue of material fact. *Celotex Corp.*, 477 U.S. at 323. Where the moving party will have the burden of proof on an issue at trial, it must affirmatively demonstrate that no reasonable trier of fact could find other than for the moving party, but on an issue for which the opposing party will have the burden of proof at trial, the party moving for summary judgment need only point out "that there is an absence of evidence to support the nonmoving party's case." *Id.* at 325; *accord Soremekun v. Thrifty Payless, Inc.*, 509 F.3d 978, 984 (9th Cir. 2007). Once the moving party meets its initial burden, the nonmoving party must set forth, by affidavit or as otherwise provided in Rule 56, "specific facts showing that there is a genuine issue for trial." *Liberty Lobby*, 477 U.S. at 250 (internal quotation marks omitted). If the nonmoving party's "evidence is merely colorable, or is not significantly probative, summary judgment may be granted." *Id.* at 249–50 (internal citations omitted).

B. Invalidity

Patents are presumed to be valid. 35 U.S.C. § 282(a). A party challenging the validity of a patent bears the burden of proving invalidity by clear and convincing evidence. *Microsoft Corp. v. i4i Ltd. P'ship*, 131 S. Ct. 2238, 2242 (2011). The parties dispute the effect of various PTO proceedings on the applicable standard of proof. However, as explained in more detail below, nothing about the initial PTO examination of the patents-in-suit or certain reexamination proceedings regarding the '808 Patent changes the presumption of validity in this case. *Microsoft Corp. v. i4i Ltd. P'ship*, 131 S. Ct. 2238, 2250 (2011) ("Nothing in § 282's text suggests that Congress meant to depart from that understanding to enact a standard of proof that would rise and fall with the facts of each case.").

III. THE '808 PATENT

Pinnaclife contends that all claims of the '808 Patent are invalid as anticipated under 35 U.S.C. § 102 or obvious under 35 U.S.C. § 103. In particular, Pinnaclife directs the Court to U.S. Patent No. 6,358,542 ("Cuomo") and an article entitled "Polyphenolic Content in Five Tuscany Cultaivars of *Olea europaea* L." ("Romani") as invalidating prior art. The Court finds that all

claims of the '808 Patent are invalid as anticipated by Cuomo, Romani, or both, and therefore the Court GRANTS Pinnaclife's Motion for Summary Judgment of Invalidity as to the '808 Patent.

A patent claim is invalid for anticipation if, among other reasons, "the invention was . . . described in a printed publication in this or a foreign country . . . , more than one year prior to the date of the application for patent in the United States," 35 U.S.C. § 102(b) (2006), or "the invention was described in . . . a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent," *id.* § 102(e) (2006).[3] A claim is anticipated under § 102, and thus invalid, "if each and every limitation is found either expressly or inherently in a single prior art reference." *Bristol–Myers Squibb Co. v. Ben Venue Labs., Inc.*, 246 F.3d 1368, 1374 (Fed. Cir. 2001) (internal quotation marks and citation omitted); *accord Eli Lilly & Co. v. Zenith Goldline Pharm., Inc.*, 471 F.3d 1369, 1375 (Fed. Cir. 2006). Put simply, "[t]hat which infringes, if later, would anticipate, if earlier." *Peters v. Active Mfg.*, 129 U.S. 530, 537 (1889) (internal quotation mark omitted).

Anticipation under § 102 is a two-step inquiry. *See Medichem, S.A. v. Rolabo, S.L.*, 353 F.3d 928, 933 (Fed. Cir. 2003). The first step is claim construction. *Id.*; *see Amazon.com, Inc. v. Barnesandnoble.com, Inc.*, 239 F.3d 1343, 1351 (Fed. Cir. 2001) ("'claim must be construed before determining its validity just as it is first construed before deciding infringement.'" (quoting *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 996 n.7 (Fed. Cir. 1995) (Mayer, J., concurring), *aff'd*, 517 U.S. 370 (1996)). The second step is a comparison of the properly construed claim to the prior art. *Medichem*, 353 F.3d at 933.

The Court previously construed the claims in its claim construction order. *See* ECF No. 67 at 40. As relevant here, the Court construed the following terms of the '808 Patent:

[3] On September 16, 2011, the America Invents Act was enacted into law. *See* Pub. L. 112-29, 125 Stat. 285 ("AIA"). The AIA fundamentally changes the rules of invalidity under 35 U.S.C. § 102. *See id.* at § 3(b)(1). The application for the '808 Patent, however, was filed before the effective date of the AIA, and therefore the prior version of § 102 applies. *See id.* at § 3(n).

Claim Language	Construction
"comprising" or "comprised of"	"including but not limited to"
the preamble "a dietary supplement" in Claims 1 and 5 of the '808 Patent	the preamble "a dietary supplement" in Claims 1 and 5 of the '808 Patent is not a claim limitation.
weight ratios claimed in the '808 Patent	the claimed weight ratios in Claims 1 and 5 of the '808 Patent apply to the "aqueous extract of olives," not to the "dietary supplement."
"aqueous extract of olives"	"an aqueous solution containing a water-soluble preparation from an olive plant," with no restriction on the process by which the "aqueous solution" is obtained.

A. Significance of the PTO Final Office Action

The '808 Patent is currently under reexamination before the PTO in *Ex Parte* Reexamination of U.S. Patent No. 6,416,808. As part of that reexamination, and after the summary judgment briefing in this case concluded, the PTO rejected all the claims of the '808 Patent in a Final Office Action. *See* ECF No. 140. The PTO examiner found claims 1-5 anticipated by Cuomo and claim 6 obvious in light of Cuomo. *Id*. The examiner further concluded that claims 1 and 4-6 were anticipated by Romani; that claim 2 was obvious in light of Romani; and that claims 3 and 4 were obvious in light of Romani in view of Cuomo. *Id*. Cuomo and Romani are the same prior art references that Pinnaclife has asserted against the '808 Patent in this case. In their briefs, the parties debate the significance of an earlier non-final action in the same reexamination as it pertains to the present motion. This debate applies to the recently issued Final Office Action as well. For the following reasons, the Court determines that neither the Final Office Action nor the non-final action is due deference, and thus the Court conducts an independent review of the parties' invalidity arguments.

As stated above, a patent is presumed valid in litigation. 35 U.S.C. § 282. In a reexamination, however, there is no such presumption. *In re Swanson*, 540 F.3d 1368, 1377 (Fed. Cir. 2008). The difference in standard of proof significantly reduces the relevance of the PTO's conclusions. *See Ethicon, Inc. v. Quigg*, 849 F.2d 1422, 1428 (Fed. Cir. 1988) ("The two forums

take different approaches in determining invalidity and on the same evidence could quite correctly come to different conclusions."). At least one other court has found that "the examiners' conclusions on reexamination are not relevant to the merits" of a summary judgment motion. *Sigram Schindler Beteiligungsgesellschaft mbH v. Cisco Sys., Inc.*, 726 F. Supp. 2d 396, 415 (D. Del. 2010). Another court has struck evidence of reexamination proceedings from consideration at summary judgment, and the Federal Circuit has ruled that such evidence should be kept from a jury. *Tesco Corp. v. Weatherford Int'l Inc.*, 750 F. Supp. 2d 780, 793–94 (S.D. Tex. 2010) (granting a motion to strike evidence of reexamination proceedings with respect to invalidity); *Callaway Golf Co. v. Acushnet Co.*, 576 F.3d 1331, 1343 (Fed. Cir. 2009).

Moreover, although the PTO office action is final, CreAgri still may file a response to the examiner that may result in the PTO's withdrawal of its invalidity conclusion. *See* 37 C.F.R. § 1.116. CreAgri also may appeal the PTO's decision to the Patent Trial and Appeal Board ("PTAB"), *see* 35 U.S.C. § 134(b), and, from there, may appeal any adverse PTAB decision to the Federal Circuit, *see* 35 U.S.C. § 141. The PTO will issue a certification canceling any claims of the '808 Patent determined to be unpatentable only after the time for appeal has expired or any appeal proceeding has terminated. *See* 35 U.S.C. § 307(a). Thus, the PTO's conclusions are "final" in name only; the PTO's adverse decisions are still subject to substantial review. Therefore, the Court reviews Pinnaclife's invalidity contentions without regard to the PTO's office actions.

B. Anticipation by Cuomo

Pinnaclife contends that Cuomo anticipates claims 1-5 of the '808 Patent. *See* Def. MSJ at 9–12. Claims 1, 2, and 5 of the '808 Patent all claim a dietary supplement by way of two limitations: (1) an "aqueous extract of olives," with (2) a weight ratio range of either hydroxytyrosol to oleoeuropein (claims 1 and 2) or hydroxytyrosol to tyrosol (claim 5). Claims 3 and 4, which depend from claim 1, each recite an additional limitation concerning the supplement form. Claim 3 requires a supplement that is "dried to provide a powder extract," and claim 4 recites a supplement that contains an extract "in the form of a tablet, capsule, pill, or confection food product." *Id*.

CreAgri does not contest that Cuomo discloses the weight ratio ranges in claims 1-5 of the '808 Patent,[4] nor does it contest that Cuomo discloses the additional limitations on supplement forms in claims 3 and 4.[5] As shown in the chart below, the parties' only dispute over whether Cuomo anticipates claims 1-5 of the '808 Patent centers on whether Cuomo discloses an "aqueous extract of olives."

Claim	Limitation	Parties' Positions
All	"an aqueous extract of olives"	*Disputed*
1, 3, 4	"containing a weight ratio of hydroxytyrosol to oleoeuropein of between about 5:1 and about 200:1."	Disclosed by Cuomo
2	"a weight ratio of hydroxytyrosol to oleoeuropein of between about 10:1 and about 100:1."	
3	"supplement is dried to provide a powder extract."	
4	"extract is in the form of a tablet, capsule, pill, or confection food additive."	
5	"containing a weight ratio of hydroxytyrosol to tyrosol of between about 3:1 and about 50:1."	

The Court is persuaded that no reasonable jury could conclude that Cuomo fails to clearly and convincingly disclose an "aqueous extract of olives." Accordingly, Pinnaclife is entitled to summary judgment that claims 1-5 of the '808 Patent are invalid as anticipated by Cuomo. Cuomo, which was filed prior to the filing date of the '808 Patent, discloses several "methods of extracting anti-oxidant compositions from olives and the by-products of olive oil production." Cuomo, at 1:8–10. Using several examples, Cuomo provides information about various compositions extracted by way of the disclosed methods. Example 4 of Cuomo describes a method for obtaining a solid antioxidant composition from an olive pulp. The procedure calls for washing the pulp with water (a polar aqueous solvent) to obtain a mixture containing the antioxidants, washing with methanol (a

[4] Table 2 of Cuomo sets forth the percentage—by weight—of hydroxytyrosol, tyrosol, and oleuropein found in what the Court ultimately determines is an "aqueous extract of olives." Cuomo, at 14:38–52.

[5] Cuomo teaches using the extracted compositions in a nutritional supplement "in any convenient form, such as a powder, a tablet or a capsule." Cuomo, at 8:63–9:8.

polar organic solvent), freezing the resulting organic solution, and evaporating the methanol, leaving a solid antioxidant composition. *Id.*, 10:63–11:6. At this point, the solid antioxidant composition is not "an aqueous extract of olives" as that term was construed by the court because it is dry.[6] But Example 11 then describes taking the antioxidant composition from Example 4, dissolving it in 80% aqueous methanol, treating it with hydrochloric acid, and analyzing the acid-treated extract for antioxidant activity and phenolic content using a variety of techniques. *Id.*, 14:13–20.

The Court concludes that Example 11's description of an 80% *aqueous* methanol solution comprising the dissolved olive pulp from Example 4 plainly describes an "aqueous solution containing a water-soluble preparation from an olive plant," and therefore no reasonable jury could conclude that the reference fails to disclose the "aqueous extract of olives" limitations of claims 1 through 5 of the '808 Patent.

In contending otherwise, CreAgri argues that a liquid extract that includes methanol, such as that disclosed in Example 11, cannot be an aqueous extract, even if that extract also includes water. *See* Pl. Opp. at 6 ("[T]he '808 Patent claims are [sic] directed towards 'aqueous extracts' are not meant to encompass 'aqueous-alcoholic extracts' of the type that are discussed in Cuomo."). The Court disagrees.

At the outset, CreAgri's argument is a new and untimely claim construction argument. CreAgri now essentially asserts that the scope of "aqueous extract" is limited to pure water extracts and therefore excludes aqueous-alcoholic extracts such as the 80% aqueous methanol extract of Cuomo's Example 11. But the Court held that an "aqueous extract of olives" is "an aqueous solution containing a water-soluble preparation from an olive plant," not, as CreAgri contends, that an "aqueous extract" is pure water. Neither party asked for a construction of "aqueous extract" that would exclude "aqueous-alcoholic" extracts. In fact, CreAgri proposed a broad construction of "aqueous extract of olives" and in doing so relied on a broad dictionary definition of "aqueous" that itself suggests "aqueous-alcoholic" extracts are merely a subset of "aqueous" extracts. *See*

[6] During claim construction, CreAgri unsuccessfully sought a construction of "aqueous extract of olives" that would have included a powdered extract, so long as it was derived from water. *See* ECF No. 67 at 24.

ECF No. 47 at 10 (relying on "the McGraw-Hill Dictionary of Scientific and Technical Terms" which "defines the word aqueous as something that is 'relating to' water."). For its part, Pinnaclife initially proposed a construction of "aqueous extract of olives" that would have resolved this issue in CreAgri's favor, contending in the parties' Joint Claim Construction Chart that "[a]s used in the '808 patent, an 'aqueous extract' is *not* an 'aqueous-alcoholic extract.'" ECF No. 43 at 3 (emphasis added). Yet Pinnaclife, possibly realizing the impact on anticipation, withdrew this proposal, *see* ECF No. 49 at 14 n.3, with no objection from CreAgri. CreAgri's attempt to relitigate the construction of "aqueous extract" at the summary judgment stage must be rejected.

Moreover, CreAgri's new claim construction argument fails on the merits. The specification of the '808 Patent makes clear that the invention includes—rather than excludes—the use of aqueous-alcoholic extracts. The following passage is key:

> The hydroxytyrosol obtained by the method *of the invention* can be administered orally or parenterally. Oral dosage forms can be in a solid or liquid form. Such dosage forms can be formulated from purified hydroxytyrosol or *they can be formulated from aqueous or aqueous-alcoholic extracts*. Regarding the latter, aqueous or aqueous-alcoholic (e.g., water-methanol or water-ethanol) extracts can be spray-dried to provide a dry powder that can be formulated into oral dosage forms with other pharmaceutically acceptable carriers. *The aqueous or aqueous-alcoholic extracts* can be formulated to contain various weight ratios of hydroxytyrosol to oleoeuropein of between 5:1 and 200:1, preferably between about 10:1 and about 100:1. *The extracts* may also be formulated to contain various weight ratios of hydroxytysol and tyrosol of between about 3:1 and about 50:1, preferably between about 5:1 and about 30:1.

'808 Patent at 7:41–56 (emphases added). In so describing the oral dosage forms "of the invention," this passage explains that forms can be "formulated from aqueous or aqueous-alcoholic extracts." '808 Patent at 7:44–45. The passage then discloses that the aqueous or aqueous-alcoholic extracts can contain the exact weight ratios claimed in the patent.

This passage provides strong evidence of the scope of the claims. More than merely a preferred embodiment, this passage describes "the invention" as a whole. *See, e.g.*, *Trading Techs. Int'l, Inc. v. eSpeed, Inc.*, 595 F.3d 1340, 1353–54 (Fed. Cir. 2010) (concluding that specification's "reference to 'the present invention' strongly suggests" that the claim carries the same meaning).

Thus, the "strong presumption against a claim construction that excludes a disclosed embodiment," *In re Katz Interactive Call Processing Patent Litig.*, 639 F.3d 1303, 1324 (Fed. Cir. 2011), applies here with even more force. Because the patentee described the invention as being formulated from aqueous-alcoholic extracts, this Court refuses to exclude aqueous-alcoholic extracts from the scope of the "aqueous extract" claim language.

CreAgri contends that this passage favors its interpretation. According to CreAgri, because the passage lists "aqueous or aqueous-alcoholic extracts," in the disjunctive, an aqueous extract must be different than an aqueous-alcoholic extract. The Court concludes that the specification's passing use of the disjunctive to connect overlapping adjectives is ambiguous at best. That ambiguity is insufficient to exclude aqueous-alcoholic extracts from the scope of the invention when the specification expressly states that aqueous-alcoholic extracts are included. Indeed, to adopt CreAgri's reading would be to improperly import a purported limitation—that an "aqueous extract" excludes an "aqueous-alcoholic extract"—from the specification into the claims. *See Phillips v. AWH Corp.*, 415 F.3d 1303, 1323 (Fed. Cir. 2005) (en banc). Accordingly, to avoid any doubt, the Court holds that its construction of "aqueous extract of olives" encompasses "aqueous-alcoholic extracts."

CreAgri makes a half-hearted argument that Cuomo still fails to disclose the claimed "aqueous extract of olives," even under a construction of an "aqueous extract of olives" that includes "aqueous-alcoholic extracts." CreAgri relies on a declaration from its expert, Dr. Bruce German, to contend that an extract that includes methanol, such as that disclosed in Example 11, cannot be an aqueous extract. *See* ECF No. 118-4 at 32–33 ¶ 65 ("German Decl."). But Dr. German fails even to acknowledge that Example 11 expressly analyzes an *aqueous* methanol solution for phenolic content. Instead, Dr. German focuses on Cuomo's Example 4, in which the phenols are first contained in a pure methanol solution. Dr. German neglects to mention that in Example 11 those phenols are dissolved in an aqueous methanol solution, a solution that Cuomo elsewhere expressly describes as a "polar *aqueous* solvent." 6:50–52; *see id.* ("Most preferably, the polar aqueous solvent is a mixture of water and methanol . . . ."). Neither CreAgri nor its expert can create an issue of fact by ignoring the most pertinent disclosure in the asserted prior art. On this

record, no reasonable jury could conclude that Example 11 fails to disclose an "aqueous extract of olives" as the Court has construed the term.

Because CreAgri has failed to show that a genuine issue of fact exists as to whether Cuomo discloses the claimed "aqueous extract of olives," and because Cuomo by clear and convincing evidence discloses all other limitations in claims 1-5 of the '808 Patent, the Court concludes that Pinnaclife is entitled to summary judgment of anticipation as to those claims.[7]

C. Anticipation by Romani

Pinnaclife separately contends that Romani anticipates claims 1, 2, 5, and 6 of the '808 Patent. Def. MSJ at 13–15. Similar to claims 1, 2, and 5—discussed above with respect to Cuomo—dependent claim 6 (together with its independent claim) covers a dietary supplement comprising (1) an aqueous extract of olives with (2) a weight ratio of hydroxytyrosol and tyrosol of between about 3:1 and about 30:1. As with Cuomo, the parties' dispute over Romani centers on whether Romani discloses the claimed "aqueous extract of olives."

The Romani reference, published over a year before the filing date of the '808 Patent, discloses the polyphenolic content of five different cultivars of olive fruits from a coastal area in Tuscany. According to the article, four of the five cultivars (Rossellino, Ciliegino, Cuoricino, and Grossolana) had never before been analyzed. *See* Romani at 964, col. 2. Crucially, Romani reports that the naturally occurring weight ratio of hydroxytyrosol to tyrosol in the Rossellino cultivar is approximately 10:1, which falls within the range of weight ratios recited in claims 5 and 6 of the '808 Patent. *See id.* at Table 2. CreAgri does not dispute that Romani discloses the weight ratio recited in claims 5 and 6 of the '808 Patent. CreAgri also concedes that Romani discloses a naturally occurring weight ratio of hydroxytyrosol to oleuropein in the Rossellino cultivar of 69:1, which falls within the ranges set forth in claims 1 and 2 of the '808 Patent. Pl. Opp. at 10. Again, the Court provides a chart for simplicity.

[7] Pinnaclife also contends that Cuomo anticipates or renders obvious claim 6 of the '808 Patent. Because the Court concludes that Pinnaclife is entitled to summary judgment that Romani anticipates claim 6, it does not reach Pinnaclife's contentions as to claim 6 and Cuomo.

Claim	Limitation	Parties' Positions
All	"an aqueous extract of olives"	*Disputed*
1	"containing a weight ratio of hydroxytyrosol to oleoeuropein of between about 5:1 and about 200:1."	Disclosed by Romani (Table 2)
2	"a weight ratio of hydroxytyrosol to oleoeuropein of between about 10:1 and about 100:1."	
5	"containing a weight ratio of hydroxytyrosol to tyrosol of between about 3:1 and about 50:1."	
6	"containing a weight ratio of hydroxytyrosol to tyrosol of between about 5:1 and about 30:1."	

The Court now turns to whether Romani discloses "an aqueous extract of olives." Pinnaclife contends that, in reporting its procedure to analyze the polyphenolic compounds in the five different olive species, Romani describes an intermediate step in which the weight ratios of polyphenolic compounds claimed in the '808 Patent exist in an "aqueous solution." The Court concludes that no reasonable jury could find otherwise. In particular, Romani recounts a procedure in which the authors took olive pulps frozen in liquid nitrogen, ground them, and then used ethanol to extract the wanted polyphenols. Romani at 964, col. 2. The authors next concentrated the ethanolic extract and rinsed it with acid water to a final volume of 250 mL, forming what Romani itself calls an "aqueous solution." *Id.* Then, the aqueous solution was "defatted"—*i.e.*, the lypophillic compounds were removed—into a concentrated "aqueous phase" of 250 mL. *Id.* at 964 col. 2–965 col. 1. Both the "aqueous solution" and the defatted "aqueous phase" plainly constitute an "aqueous extract of olives" under the Court's claim construction.

CreAgri does not dispute that the expressly disclosed "aqueous solution" and "aqueous phase" compositions in Romani constitute an "aqueous extract of olives." Instead, CreAgri contends that the end result of the Romani process is not an "aqueous extract" because the authors ultimately analyzed the polyphenolic content of the olives using a "liquid-solid extraction" process that used two additional solvents—ethyl acetate and acid methanol—to create dry fractions from the aqueous solution. *See* Pl. Opp. at 9.

Taking CreAgri's description of these later steps as true, the steps nevertheless fail to create a material issue of fact as to whether the solution disclosed in Romani is an "aqueous extract of olives." Once again, CreAgri's argument disregards this Court's claim construction ruling. The Court has already concluded that the construction of "aqueous extract of olives" is not tied to any particular process, a construction that CreAgri wanted. *See* ECF No. 67 at 31–32. Accordingly, Romani's disclosure of an "aqueous solution" and "aqueous phase" is an express disclosure of the "aqueous extract" limitation regardless of whether later steps in the extraction process reduce those preparations to a solid. Romani does not suggest, and CreAgri does not contend, that the polyphenolic profiles change depending on the phase of the described olive extracts. To the contrary, Romani discloses using the dry fractions to determine the polyphenolic content of the original olive. The premise of this procedure is that the intermediate steps in the measurement process (during which the authors obtain the aqueous extract of olives) do not alter the hydroxytyrosol, tyrosol, and oleuropein levels naturally found in the Rossellino cultivar, levels that indisputably fall within the ratios stated in claims 1–2 and 56 of the '808 Patent.

CreAgri also contends that Pinnaclife's arguments with respect to Romani must meet an "'enhanced'" burden of proof because "[t]he Romani reference was already cited to the PTO during the initial prosecution of the '808 patent." Pl. Opp. at 8 (citing *Creative Compounds, LLC v. Starmark Labs.*, 651 F.3d 1303, 1313 (Fed. Cir. 2011)). To the extent CreAgri is arguing that Pinnaclife's proof must be more than clear and convincing, the Federal Circuit has recently rejected that argument. *See OSRAM Sylvania, Inc. v. Am. Induction Techs., Inc.*, 701 F.3d 698, 705 (Fed. Cir. 2012) ("While prior consideration of a reference during prosecution may carry some weight, the burden to prove invalidity does not change; at all times, it remains a showing 'by clear and convincing evidence.'") (quoting *Microsoft Corp.*, 131 S. Ct. at 2242). Moreover, "[w]hether the examiner actually considered this issue can only be determined by reviewing the prosecution history." *In re NTP, Inc.*, 654 F.3d 1268, 1278 (Fed. Cir. 2011). Yet there is no evidence from the prosecution history that the examiner—or anyone at the PTO—ever considered Romani during prosecution of the '808 Patent. In fact, the title page of the '808 Patent cites 22 references, including 3 that were cited by the examiner, and Romani was not among any of them. The'808

Patent specification also includes a "References" section. '808 Patent at 1:16–64. This "References" section does include Romani, as one of 24 unique references that do not appear on the '808 Patent's title page.[8] The only description of Romani in the entire '808 Patent, however, is in the specification's citation of Romani—along with 2 other articles—to describe possible "[a]dditional purification methods." *Id.* at 7:23–27. Romani is never cited in the '808 Patent's specification as containing any information on polyphenolic weight ratios. Therefore, the '808 Patent provided no indication to the examiner that Romani discloses polyphenolic weight ratios: Romani was cited in a list of 25 other "References" in the body of the specification, the '808 Patent only mentioned Romani later in the specification as being relevant for another purpose, and even there Romani was second in a string cite of three references. As a result, it is unlikely the PTO examiner ever considered Romani as a potentially invalidating reference. With the prosecution history being devoid of any mention of Romani—at least until the patent examiner in the current *Ex Parte* Reexamination found some of the '808 Patent's claims invalid as anticipated by Romani[9]—the Court simply cannot draw an inference of validity in CreAgri's favor sufficient to overcome the plain anticipating disclosure of Romani.

In sum, Pinnaclife has established the absence of an issue of material fact as to the anticipation of claims 1–2 and 5–6 of the '808 Patent by the Romani reference.

As to the claim elements added in dependent claims 3 and 4, the parties agree that Romani does not disclose these limitations. Pinnaclife makes a compelling argument that claims 3 and 4 are obvious in light of Romani in view of Cuomo, but given that the Court found above that claims 3 and 4 are anticipated by Cuomo, the Court declines to reach Pinnaclife's obviousness contention.

D. Whether the '808 Patent claims unpatentable natural phenomena under section 101

Pinnaclife has also moved for summary judgment of invalidity on the grounds that the '808 Patent claims natural phenomena and therefore is invalid under 35 U.S.C. § 101. As all claims of

[8] The '808 Patent's "References" section includes 25 total references: 24 unique references including Romani, and one other reference that also appears on the title page.

[9] Note that, as discussed in Section II.A, the Court does not rely on the PTO decision here. The Court draws its independent conclusions based on a review of the evidence in this case.

the '808 Patent are invalid under section 102 in light of either Cuomo or Romani, the Court declines to address the parties' arguments as to section 101.

IV. THE '599 PATENT

The '599 Patent claims methods of treating a broad range of inflammatory conditions using various forms of hydroxytyrosol. Pinnaclife challenges the validity of all claims of the '599 Patent on written description, enablement, and utility grounds, contending that "the specification of the '599 Patent does not support or enable the use of any hydroxytyrosol-rich composition to treat inflammation conditions claimed because the specification provides no data whatsoever to support the anti-inflammatory effects of the claimed olive-derived preparations." Def. MSJ at 19. The Court is satisfied that Pinnaclife has met its burden to show the absence of a genuine dispute as to any material issues for all three doctrines and therefore GRANTS Pinnaclife's Motion for Summary Judgment of Invalidity as to the '599 Patent.

A. The "Written Description" Requirement of Section 112

1. Applicable Law

Under 35 U.S.C. § 112(a), a patent specification must contain "a written description of the invention."[10] Under this written description requirement, the specification "must clearly allow persons of ordinary skill in the art to recognize that the inventor invented what is claimed." *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (en banc) (internal quotation marks and alterations omitted). This test requires "an objective inquiry into the four corners of the specification from the perspective of a person of ordinary skill in the art" to determine whether the specification shows that "the inventor actually invented the invention claimed." *Id.* Although "[c]ompliance with the written description requirement is a question of fact," it is, like most factual questions, "amenable to summary judgment in cases where no reasonable fact finder could return a verdict for the non-moving party." *PowerOasis, Inc. v. T-Mobile USA, Inc.*, 522 F.3d 1299, 1307 (Fed. Cir. 2008).

[10] The passage of the AIA did not materially affect the written description, utility, or enablement requirements. The AIA redesignated the provisions of section 112, such that what was previously designated the first paragraph of section 112 is now designated section 112(a). *See* AIA § 4(c). For convenience, the Court refers to the redesignated provision of section 112.

2. Analysis of the '599 Patent

The Court now looks to the '599 Patent and the parties' submissions to determine if Pinnaclife has demonstrated that no reasonable fact finder could conclude that the specification supports the claimed invention. Pinnaclife argues that the '599 Patent includes no data supporting the use of hydroxytyrosol and oleuropein, either in the ratios recited in independent claim 1 and its dependent claims or in the "substantially purified" mixture recited in independent claim 16, to treat the inflammatory conditions set forth in the claims. Def. MSJ at 22.

The "level of detail required to satisfy the written description requirement varies depending on the nature and scope of the claims and on the complexity and predictability of the relevant technology." *Ariad*, 598 F.3d at 1351 (citing *Capon v. Eshhar*, 418 F.3d 1349, 1357–58 (Fed. Cir. 2005)). In this case, the claims have a chemical nature. "[T]he chemical arts have long been acknowledged to be unpredictable," *Boston Scientific Corp. v. Johnson & Johnson*, 647 F.3d 1353, 1370 (Fed. Cir. 2011) (Gajarsa, J., concurring) (internal quotation marks omitted); *see Spectra-Physics, Inc. v. Coherent, Inc.*, 827 F.2d 1524, 1533 (Fed. Cir. 1987), and patents in that field—including patents directed to treating inflammation—are often found to lack a sufficient written description, *see, e.g.*, *University of Rochester v. G.D. Searle & Co.*, 358 F.3d 916 (Fed. Cir. 2004). In addition, the scope of the two independent claims in the '599 Patent is broad.[11] Broad claim scope requires more supporting detail because the recitation in the specification must "demonstrate that the inventor possesses the full scope of the invention." *LizardTech, Inc. v. Earth Resource Mapping, Inc.*, 424 F.3d 1336, 1345 (Fed. Cir. 2005).

Each independent claim asserts a therapy effective against several different ailments. Claim 1 recites a method of treating three conditions: coronary inflammation, bronchial inflammation, and neuro inflammation. Claim 16 recites a method of treating seven specified inflammatory conditions: "delayed type hypersensitivity reaction, psoriasis, an autoimmune disease, organ transplant, pain, fever, and tissue graft rejection." '599 Patent at 20:49–51. The claimed range of

[11] All the dependent claims of the '599 Patent (claims 2-15) depend from claim 1. *See* '599 Patent 20:6–41. The dependent claims do not limit the claimed scope of the therapeutic effect of claim 1, and CreAgri does not argue that any dependent claims are adequately described notwithstanding the status of claim 1. Accordingly, the fate of claim 1 will dictate whether the dependent claims survive summary judgment on written description grounds.

dosage levels is also broad. Both independent claims recite a dosage level for each respective ailment ranging from about 0.1 mg/kg body weight to 2000 mg/kg body weight, meaning that, for an average male of approximately 80 kg, the claimed treatment is effective for all conditions at a daily dosage level anywhere from 8 mg to 160,000 mg. Various dependent claims narrow that daily dosage to between about 0.3 mg/kg and 1 mg/kg (claim 10) and about 0.6 mg/kg (claim 11).

a. The specification fails to show that Dr. Crea possessed the full scope of the invention

A person of ordinary skill in the art would be unable to conclude from the specification that the inventor of the '599 Patent possessed the claimed invention.[12] Although the specification does describe the compositions used by the claimed methods in some detail—including how to obtain them from olive vegetation water—the specification repeatedly disclaims the novelty of obtaining the compositions themselves. *See*, *e.g.*, *id.* at 5:54–55 ("The olive-derived phenolic compounds employed herein can be prepared by a number of methods known in the art."). Instead, the specification conclusively reveals that the inventor sought to claim a method of treating inflammation based on no more than a hope that olive-derived compositions would one day be used effectively to treat inflammation caused by a wide variety of factors. As the inventor himself conceded during his deposition, this patent was filed with the anticipation that the compositions could be used as claimed, but without data showing as much. *See* Marshall Decl. Ex. C at 174:7–23 ("Crea Dep."), ECF No. 161-3 ("A: I learned early in my career that you can file patents, they are

[12] The parties disagree as to the level of ordinary skill in the art. CreAgri's expert, Dr. German, expresses his preference for a relatively low level of skill, finding one having ordinary skill in the art to be "someone with a bachelor's degree or higher in Food Science or related Biological fields related to diet and health and/or several years of experience in the life sciences research industry." German Decl. ¶ 28. In contrast, Pinnaclife's expert, Dr. Visioli, asserts that one with ordinary skill in the art has "a Ph.D. in the biological sciences, including biology, chemistry, biochemistry, biotechnology, nutritional biology, food science, or a similar field, and at least 2 years of experience studying phenolic compounds of olives and the health effects of the Mediterranean diet." Visioli Rep. ¶ 15. Without taking a position on the issue, the Court assumes for the purposes of Pinnaclife's Motion for Summary Judgment of Invalidity that CreAgri's proposed lower level of ordinary skill in the art applies. Because the specification provides no data—or even a study design—as to most of the claimed treatments, the Court's analysis on written description does not turn on the parties' debate over the level of ordinary skill in the art. Therefore, the Court finds all claims of the '599 Patent invalid despite using CreAgri's proposed lower level of ordinary skill in the art.

prophetic. . . . Q: You anticipate that this would work? A: Right. Q: But you don't actually have the data yet showing that it would work? A: Yeah. . . . .").

. The prophetic approach to patenting is not proper absent some indication that the named inventor has "actually perform[ed] the difficult work of 'invention'—that is, [he has] conceive[d] of and complete[d] the final invention." *Ariad*, 598 F.3d at 1351. A description that amounts "to no more than a 'wish' or 'plan' for obtaining [the claimed invention]" fails the written description requirement. *Id.* at 1350 (citing *Fiers v. Revel*, 984 F.2d 1164, 1170–71 (Fed. Cir. 1993)). Indeed, very little of the '599 Patent's specification is directed to treating inflammation using olive-derived phenols at all. Only about two-and-a-half columns of the nineteen-column specification discusses inflammation. *See* '599 Patent, 12:30–14:62 (subsection E, entitled "Treatment of Inflammation or Inflammation-Associated Conditions"). Although the claims are directed to methods of treating inflammations of various causes, the primary aspect discussed in the specification is "a method of treating an AIDS-associated *neurological* disorder," *id.* at 5:31–32 (emphasis added), and "[a]dditional *neurological* diseases and disturbances contemplated for treatment by the method of the invention," *id.* at 10:23–24 (emphasis added). *See also id.* at 2:33–36 ("[I]t is an object of the invention to provide, in one aspect, a method of treating an AIDS-associated neurological disorder in a subject in need of such treatment."); 8:1–63 (discussing HIV-1 Associated Dimentia); *id.* at 8:64–9:12 (HIV-Associated Myelopathy); 9:13–9:46 (peripheral neuropathy, "a very common and disabling problem encountered in HIV infection."); 9:47–10:6 (Cytomegalovirus, "a frequent secondary viral infection in AIDS patients"); 10:7–21 (Progressive Multifocal Leukoencephalopathy, "a lethal secondary viral infection mostly occurring in AIDS patients with advanced immunodeficiency"); *see also id.* at 11:44–12:29 (methods of biological testing AIDS-associated neurological disorders).[13]

[13] The '599 Patent suggests that olive-derived phenols can also treat "Alzheimer's disease; Parkinson's disease; motor neuron diseases such as amyotrophic lateral sclerosis (ALS), Huntington's disease and syringomyelia; ataxias, dementias; chorea; dystonia; dyslinesia; encephalomyelopathy; parenchymatous cerebellar degeneration; Kennedy disease; Down syndrome; progressive supernuclear palsy; DRPLA, stroke or ischemic injuries; thoracic outlet syndrome, trauma; electrical brain injuries; decompression brain injuries; multiple sclerosis; epilepsy; concussive or penetrating injuries of the brain or spinal cord; brain injuries due to exposure of military hazards such as blast over-pressure, ionizing radiation, and genetic neurological conditions." 10:23–38.

Even the subsection in the specification discussing inflammation does not explain why the inventor believed that olive-derived compositions were likely to treat any (much less all) the claimed conditions. Instead, that subsection largely discusses inflammation and its various causes generically and abstractly. *See id.* at 12:42–46 ("Typically, inflammation is a very localized response that serves to expulse, attenuate by dilution, and isolate the damaging agent and injured tissue. The body's response becomes an agent of disease when it results in inappropriate injury to host tissues . . . ."). The specification acknowledges in this section that the "composition of this invention depends on a variety of factors" and thus "the route and frequency of administration, and the particular compound employed . . . may vary widely." *Id.* at 14:26–32. Yet at no point does the specification explain why the inventor believed that the hydroxytyrosol and oleuropein compositions recited in the claims would counteract any of the listed causes of inflammation. The closest the specification comes to describing the method of treatment recited in the claims is a near verbatim (and conclusory) reproduction of the claim language itself. *See id.* at 13:10–43 ("The method [of the present invention] includes administering to the subject a pharmaceutically effective amount of substantially purified hydroxytyrosol or a substantially purified mixture of hydroxytyrosol and oleuropein."); 14:33–37 ("The pharmaceutical compositions may contain active ingredient in the range of about 0.1 to 2000 mg/kg body weight, preferably in the range of about 0.3 to 50 mg/kg and most preferably about 0.6 mg/kg."). But "generic claim language appearing *in ipsis verbis* in the original specification does not satisfy the written description requirement if it fails to support the scope of the genus claimed." *Ariad*, 598 F.3d at 1350. Here, neither the claims nor the specification discloses that the inventor possessed a treatment for inflammation caused by any of the claimed conditions, much less all of them.

b. The specification's examples fail to support the claimed invention

In contending that the specification adequately supports the claimed invention, CreAgri points to five studies described in the specification. Pl. Opp. at 19 (citing '599 Patent, 16:21–19:24). Pinnaclife responds that these studies are bare research proposals that cannot demonstrate that Dr. Crea possessed the invention. CreAgri primarily relies on these studies as prophetic; the specification reports only limited "[i]nitial results" for one of the five proposals. '599 Patent,

18:36–38. "Prophetic examples are routinely used in the chemical arts, and they certainly can be sufficient to satisfy the written description requirement." *Ariad*, 598 F.3d at 1357. A disclosure is insufficient, however, when it "is not so much an 'example' as it is a mere mention of a desired outcome." *Id*. The Court finds that the studies outlined in the specification are mere mentions of a desired outcome rather than permissible prophetic examples, and thus, the specification's examples fail to support the claimed invention.

The first study—by far the most robustly outlined study in the patent—is described in three separate "Examples." *See* '599 Patent, 16:40–18:38. These examples outline study procedures, data analysis procedures, and subject selection procedures, respectively, for a "pilot safety and tolerability" study of "the active ingredient"[14] in HIV-positive men and women "with signs and symptoms of HIV-associated cognitive-motor syndrome or frank [AIDS dementia complex]." *Id*. at 16:45–18:38. The specification discloses that "initial results" from this study "showed a statistically significant favorable change in 8-isoprostane levels in the urine." *Id.* at 18:36–38. Beyond this statement, the '599 Patent provides no results, either realized or predicted.

This study provides insufficient support for the full scope of the claimed method of treating inflammation. The study is directed to the AIDS-related neurological treatment discussed in the specification, not the treatment of the various causes of inflammation recited in the claims. *See*, *e.g.*, *id.* at 16:45–47 (proposing participants who suffer from "HIV-associated cognitive dysfunction"); *id.* at 11:59–63 (describing Example 1 as using an "exemplary *neuropsychological* test" (emphasis added)). Moreover, the limited finding regarding a change in 8-isoprostane levels in the urine has little relevance to the full scope of the claimed therapy. Independent claim 1 uses isoprostane found in cerebrospinal fluid ("CSF") as a marker for the purposes of administering the therapy, whereas the study measures isoprostane in the urine, without explaining how the two are related. Assuming for purposes of this motion that a person of ordinary skill in the art would understand the two isoprostane levels to be sufficiently related, the study's small dataset as to

[14] The example specifies the active ingredient to be "20 mg total phenols" but does not refer explicitly to hydroxytyrosol or oleuropein, the two substances named in the independent claims. '599 Patent at 16:46. The Court assumes for purposes of Pinnaclife's summary judgment motion that a person of ordinary skill in the art would understand the examples to refer to the compositions recited in the claims.

isoprostane levels does not support the effectiveness of the patented therapy as to the full scope of the claims (including the other two ailments recited in claim 1 and the other six claimed in claim 16). Acknowledging the small sample size ("up to 32 subjects"), the specification itself states that this study is to be used only as "a pilot safety and tolerability study" and that "statistical significance is not expected for the primary efficacy endpoint in this small study." *Id.* at 18:8–13. The '599 Patent's own predicted result, therefore, is that the study will not serve to demonstrate the efficacy of the therapy, and the Court will not read the study's abbreviated findings as more persuasive than the patentee believed possible.

Example 4 of the '599 Patent briefly sets out the remaining four studies, outlining the basic procedures for three human models and one mouse model for testing the effectiveness of an "active agent"[15] with regard to arthritis. *Id.* at 18:44–19:17. Again, these proposed studies cannot describe the full scope of the claims, as arthritis is only relevant to two of the claimed seven ailments in claim 16 and none of the three in claim 1. Moreover, these study designs fail to disclose any results whatsoever, whether realized or predicted. *See id*. The '599 Patent outlines the experiments in one or two short paragraphs of description each; this "example" reads like an internal draft study proposal, not a written description of the invention for the public. *See id.* at 18:44–48 ("Test a group of individuals with Rheumatoid Arthritis and a group with Osteoarthritis with the stress reactivity protocol, before and after 4 weeks of active agent (20 mg total phenols) supplementation and compare to controls over the same time period with no supplementation."); *id.* at 18:51–54 ("Test individuals with Rheumatoid Arthritis, before and after 10 weeks of active agent supplementation and compare to a group doing water aerobic exercise and a control group that does no intervention."); *id.* at 18:58–59 ("Test individuals with Rheumatoid Arthritis, with and without active agent supplementation for four weeks . . . ."); *id.* at 18:63–65 ("Evaluate increasing concentrations of active agent in a collagent-induced arthritis mouse model at 1.3 mg, 13 mg and 130 mg/mouse; with and without Cox-2 inhibitors."). These study proposals in fact demonstrate

[15] As discussed in note 8, *supra*, the specification defines "active agent" as "20 mg total phenols." '599 Patent at 18:46; *see also id.* at 18:52, 18:58, 18:63 (referencing "active agent" in model description).

that the inventor had not yet done the difficult work of inventing the claimed therapy. They do nothing to demonstrate that the inventor possessed the invention.

c. The '599 Patent does not inherently disclose a sufficient description of the claimed invention to a person of ordinary skill in the art

CreAgri also contends that the '599 Patent inherently satisfies the written description requirement because "the general principle that olive phenols, such as hydroxytyrosol, had anti-inflammatory properties was known by others in the art." Pl. Opp. at 19. In support of this statement, CreAgri directs the Court to its expert's declaration and five prior art references cited in the '599 Patent. Considering each in turn, the Court finds that none of this evidence raises a triable issue of fact.

Although a patentee may satisfy the written description requirement by an inherent disclosure, "'the missing descriptive matter must necessarily be present in the application's specification such that one skilled in the art would recognize such a disclosure.'" *PowerOasis*, 522 F.3d at 1306 (quoting *Tronzo v. Biomet, Inc.*, 156 F.3d 1154, 1159 (Fed. Cir. 1998)) (alteration omitted). In other words, the written description requirement "is 'not a question of whether one skilled in the art *might* be able to construct the patentee's [invention] from the teachings of the disclosure . . . . Rather, it is a question whether the application necessarily discloses that particular [invention].'" *Id.* (quoting *Martin v. Mayer*, 823 F.2d 500, 505 (Fed. Cir. 1987) (emphasis in original); *see id.* at 1306–07 ("[T]hat the [claim element] may be obvious from the disclosure is not enough[.]") (citing *TurboCare Div. of Demag Delaval Turbomachinery Corp. v. Gen. Elec. Co.*, 264 F.3d 1111, 1118–20 (Fed. Cir. 2001)).

CreAgri cites Dr. German's declaration, which states that "it is inherent in the description of the patent and the appropriate markers to be measured that these be applied to a susceptible population using markers that were well understood by persons of skill in the art." German Decl. ¶ 95. Dr. German does not cite to the specification for this proposition, but presumably he refers to the paragraph in the specification that lists the relevant biomarkers. *See* '599 Patent at 13:30–42 ("The marker or the clinical symptom may include any number of markers or clinical symptoms which are generally known in the art to be associated with inflammation. Preferably, the symptoms

and markers are associated with specific types of inflammation. These include (i) the symptoms and markers in joint pain and swelling in the case of joint inflammation; (ii) elevated levels of C-reactive protein in the case of coronary inflammation; (iii) respiratory distress in the case of bronchial inflammation; and (iv) elevated CSF levels of isoprostanes or functional or psychofunctional indicators in the case of neuro-inflammation. The marker may be a cytokine, such as TNF-α, interleukin-1, interleukin-6, and/or interleukin-8. Other markers include corticotrophin, cortisol and/or prolactin."). Because the '599 Patent's specification at most discloses how to measure whether the claimed treatment works, not whether the claimed treatment in fact works, the Court finds that the '599 Patent's disclosure of the relevant biomarkers is insufficient to create an inherent disclosure of the full scope of the claimed invention.

Crucially, CreAgri's expert does not opine that the '599 Patent inherently discloses the claimed method of treatment. To the contrary, Dr. German acknowledges in the same paragraph on which CreAgri relies that inflammation is a "complex and diverse process[]." German Decl. ¶ 95. Dr. German goes on to explain that "[t]he patent discloses reasonable and appropriate biomarkers." *Id*. These biomarkers, according to the specification, are used to detect whether an individual may have an inflammatory condition. '599 Patent at 13:17–20. And claim 1, for example, uses these same biomarkers to determine whether the claimed treatment has achieved its therapeutic effect. But CreAgri never points to anywhere in the specification showing that the claimed treatment does have its therapeutic effect. Thus, at most, Dr. German's declaration states that the '599 Patent inherently discloses how to measure *whether* the treatment works as claimed, not that the treatment *does* work as claimed. That statement fails to create an issue of material fact as to whether the specification actually or inherently discloses that the inventor possessed the claimed invention.

In addition, CreAgri attempts to create an issue of fact by pointing to the '599 Patent specification's incorporation of five prior art references that discuss hydroxytyrosol's anti-inflammatory effect. None of those references, however, demonstrate the medical efficacy of hydroxytyrosol, hydroxytyrosol together with oleuropein, or olive plant extract having a given ratio of hydroxytyrosol to oleuropein, for treating inflammation arising out of the numerous causes recited in the claims of the '599 Patent. The Court addresses each of the references in turn.

- The Fehri reference, *see* Lee Decl. Vol. 2, Ex. 14, ECF No. 118-5, reported tests of the anti-inflammatory effects of olive leaf extract in mice but without reference to hydroxytyrosol or oleuropein. Moreover, the article concludes that the observed anti-inflammatory effect "could be investigated" in therapeutics, not that olive leaf extract has a therapeutic use.
- The Ragione reference, *see* Lee Decl. Vol. 3, Ex. 15, ECF No. 118-6, reported tests of hydroxtyrosol for apoptogenic activity and, although it found success with respect to a leukemia-based cell line, the article concluded that two colon cell lines, in contrast, "were completely resistant to the apoptogenic capability of DPE" and therefore "the programmed cell death due to the olive oil phenol is specific for cell phenotype," *id.* at 735–36. In other words, the article was unable to draw a conclusion about the general anti-inflammatory effect of hydroxytyrosol, much less hydroxytyrosol's anti-inflammatory effect on the various ailments recited in the claims of the '599 Patent.
- The Visioli reference, authored by Pinnaclife's expert, *see* Marshall Decl. Ex. D, reported tests of olive mill wastewater extract but made only the following conclusion:

> OMWW [olive mill wastewater] extracts *could* . . . decrease the production of pro-inflammatory factors. Additional studies are needed to verify if such anti-inflammatory effects could also take place in vivo and the exact enzymatic target of the bioactive compounds. . . . . OMWW are rich in antioxidant compounds that could be . . . employed . . . , following appropriate trials to evaluate their safety and efficacy, as prophylactic agents in the prevention of certain radical-induced human diseases.

Id. at 3401 (emphasis added). Thus, like the '599 Patent itself, the Visioli reference is, at best, prophetic only.

- The Kohyama and Petroni references, *see* Marshall Decl. Vol. 3, Exs. L–M, ECF No. 103-4, provided *in vitro* results suggesting that enzymes involved in inflammatory processes could be inhibited by hydroxytyrosol, but both also stressed the need for *in vivo* testing. *Id.* Ex. L at 350; *Id.* Ex. M at 158–59.

These references all reflect a field actively exploring the possibility of the anti-inflammatory use of hydroxytyrosol and oleuropein, as well as substances known to contain

hydroxytyrosol and oleuropein, but not at the point of inherently appreciating the use of these substances to treat coronary, bronchial, and neuro inflammation (claim 1) or inflammation caused by delayed type hypersensitivity reaction, psoriasis, and autoimmune disease, organ transplant, pain, fever, and tissue graft rejection (claim 16).

***

In sum, the cited prior art does not suggest that persons having ordinary skill in the art would understand the specification's disclosure to describe that the inventor invented what was claimed. The study outlines disclosed in the specification itself all reveal that the inventor's statements of invention are, at best, premature. The written description requirement prohibits inventors from "'prempt[ing] the future before it has arrived,'" *Billups-Rothenberg, Inc. v. Associated Regional & University Pathologists, Inc.*, 642 F.3d 1031, 1036 (Fed. Cir. 2011) (quoting *Fiers v. Revel*, 984 F.2d 1164, 1171 (Fed. Cir. 1993)), yet here the inventor left "[t]he actual inventive work" of generating the claimed treatment "for subsequent inventors to complete," *Centocor Ortho Biotech, Inc. v. Abbott Labs.*, 636 F.3d 1341, 1353 (Fed. Cir. 2011). Accordingly, the claims of the '599 Patent are invalid for failure to meet the written description requirement of section 112.

B. The "Enable . . . To Use" Requirement of Section 112(a)

1. Applicable Law

As the *en banc* Federal Circuit has noted, "written description and enablement often rise and fall together." *Ariad*, 598 F.3d at 1352. "In order to satisfy the enablement requirement of section 112, an applicant must describe the manner of making and using the invention 'in such full, clear, concise, and exact terms as to enable any person skilled in the art . . . to make and use the same . . . .'" *Rasmusson v. SmithKline Beecham Corp.*, 413 F.3d 1318, 1322 (Fed. Cir. 2005) (quoting 35 U.S.C. § 112). "The how to use prong of section 112 incorporates as a matter of law the requirement of 35 U.S.C. § 101 that the specification disclose as a matter of fact a practical utility for the invention." *In re Ziegler*, 992 F.2d 1197, 1200 (Fed. Cir. 1993). Thus, "[i]f a patent claim fails to meet the utility requirement because it is not useful or operative, then it also fails to

meet the how-to-use aspect of the [section 112] enablement requirement." *In re '318 Patent Infringement Litig.*, 583 F.3d 1317, 1324 (Fed. Cir. 2009) (emphasis omitted).

Because "[e]nablement, or utility, is determined as of the application filing date," *In re Brana*, 51 F.3d 1560, 1567 n.19 (Fed. Cir. 1995), an invention will not be considered useful for the purposes of section 101 where, at the time of filing, "there is a complete absence of data supporting the statements which set forth the desired results of the claimed invention"—even if the invention is later proven useful or operable. *Rasmusson*, 413 F.3d at 1323 (quotations omitted); *see also Brenner v. Manson*, 383 U.S. 519, 535 (1966) ("Congress intended that no patent be granted on a chemical compound whose sole 'utility' consists of its potential role as an object of use-testing.").

Furthermore, "[i]f mere plausibility were the test for [enabling disclosures of utility] under section 112, applicants could obtain patent rights to 'inventions' consisting of little more than respectable guesses as to the likelihood of their success." *Rasmusson*, 413 F.3d at 1325. But the Patent Act does not provide for the patenting of mere research proposals or hypotheses. *In re '318 Patent Infringement Litig.*, 583 F.3d at 1324. "[A] patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion." *Brenner*, 383 U.S. at 536.

"In the context of determining whether sufficient utility as a drug, medicant, and the like in human therapy has been alleged, it is proper . . . to ask for substantiating evidence unless one with ordinary skill in the art would accept the allegations as obviously correct." *Rasmusson*, 413 F.3d at 1323 (internal quotation marks omitted). In this regard, "[t]he full scope of the claimed invention must be enabled," meaning that a "patentee who chooses broad claim language must make sure the broad claims are fully enabled." *Sitrick v. Dreamworks, LLC*, 516 F.3d 993, 999 (Fed. Cir. 2008). Regardless of the breadth of the claims, "[t]ypically, patent applications claiming new methods of treatment are supported by test results." *In re '318 Patent Infringement Litig.*, 583 F.3d at 1324. However, "testing need not be conducted by the inventor," and "human trials are not required." *Id.*

Whether a disclosure is enabling under 35 U.S.C. § 112(a) is a question of law based on underlying factual inquiries. *See Enzo Biochem, Inc. v. Calgene, Inc.*, 188 F.3d 1362, 1369 (Fed. Cir. 1999). Whether an invention is operative, and hence has utility within the meaning of § 101,

appears to be one of those factual inquiries. *See In re Dash*, 118 F. App'x. 488, 490 (Fed. Cir. 2004) (citing *In re Swartz*, 232 F.3d 862, 863 (Fed. Cir. 2000)).

2. Analysis of the '599 Patent

A patent is deemed useful where "one skilled in the art would accept without question statements as to the effect of the claimed drug products." *Rasmusson*, 413 F.3d at 1323 (alternations and internal quotation marks omitted). Alternatively, there must be some quantum of data or reasoning that supports the inventor's contention that a therapy operates as claimed. *See In re '318 Patent Infringement Litig.*, 583 F.3d at 1326. The Court will consider each of these alternatives with respect to the '599 Patent.

a. One skilled in the art would not, at the time of filing, accept without question the '599 Patent's bare assertion of the claimed treatments' effectiveness

Pinnaclife argues that one having ordinary skill in the art would not accept an assertion that hydroxytyrosol and oleuropein have therapeutic anti-inflammatory qualities. The Court agrees. On this point, Pinnaclife's expert, Dr. Francesco Visioli,[16] provides clear and uncontroverted evidence: "[b]y 2002, no researcher working in the field of olive-derived polyphenols had published reliable data establishing that either hydroxytyrosol or oleuropein showed *in vivo* anti-inflammatory activity."[17] Marshall Decl. Ex. N. ("Visioli Rep.") ¶ 33, ECF No. 103-5. "[I]n the 1999-2002 time period, anti-inflammatory activity could not be inferred from research showing that olive-derived polyphenols exhibit antioxidant activity." *Id.* ¶ 34. That is, Dr. Visioli contends that the compounds in question were not known at the time of filing to provide the alleged therapeutic effects and their known antioxidant properties were not grounds for inferring such therapeutic effects.

[16] CreAgri has separately moved to disqualify Dr. Visioli based on a purported conflict of interest. *See* ECF No. 80. The Court will issue a separate order concluding that CreAgri has failed to show that Dr. Visioli should be disqualified from assisting Pinnaclife in this case.

[17] "*In vivo*" activity refers to activity "within living organisms," whereas "*in vitro*" activity refers to activity in "artificial environments outside living organisms (such as in a test tube or culture media)." *In re '318 Patent Infringement Litig.*, 583 F.3d at 1324 n.7.

CreAgri's expert, Dr. German, protests that he is "unable to determine the evidentiary basis" of the second of these two opinions. German Decl. ¶ 55. But Dr. German does not reject or otherwise controvert either of Dr. Visioli's opinions that the therapeutic effect of olive-derived polyphenols had not been established in the art. *See id.* Instead, he cites two articles written by Dr. Visioli that Dr. German contends "assert that antioxidant activity was *related* to anti-inflammatory activity in 2001 and 2002." German Decl. ¶ 55 (emphasis added). CreAgri has not provided a copy of these articles to the Court, and Dr. German's description of them fails to create an issue of fact as to whether a person of ordinary skill in the art would accept the claimed therapeutic effect of olive-derived phenolic compounds, in humans or other animals.

To avoid any doubt, the Court independently obtained and examined the two articles authored by Dr. Visioli and cited by Dr. German, and has discovered that neither establishes a recognition in the art of the therapeutic effects of olive-derived polyphenols.

The first article, "Antiatherogenic Components of Olive Oil," summarizes in three pages other studies. Francesco Visioli and Claudio Galli, *Antiatherogenic Components of Olive Oil*, Current Atherosclerosis Rep., Jan. 2001, at 64–67. The article expresses hope that phenolic compounds in olives could have therapeutic effects, but it provides no evidence whatsoever of those effects.

The second article, entitled "Antioxidant and Other Biological Activities of Phenols from Olives and Olive Oil," supplies new and successful experimental results, but its ultimate conclusion runs against CreAgri's position that a person of ordinary skill in the art would accept the claimed therapeutic effect of the claimed treatment methods. Francesco Visioli, et al., *Antioxidant and Other Biological Activities of Phenols from Olives and Olive Oil*, Med. Res. Rev., Jan. 2002, at 65–75. The article summarizes that "[t]o date, these data represent the first, albeit limited, experimental evidence of a healthful effect of olive oil components on human health. In the future, availability of pure—or even labeled—compounds in adequate quantities and development of appropriate methodologies will further clarify the metabolic fate of phenolic micronutrients, including those of olive oil." *Id.* at 71.

These statements, albeit hopeful that later research will prove a link between phenols in olives and better health, demonstrate that the link was not accepted in the art at the time of the '599 Patent's filing. Instead, this article represents some of the first steps of investigating which elements of the Mediterranean diet produce beneficial health effects. The article concludes that "[i]t is in fact difficult to single out an individual component of [the Mediterranean] diet and correlate it with the observed lower incidence of CHD [coronary heart disease] and certain cancers." *Id*. at 72. Therefore, not only are Dr. German's assertions insufficient to create a fact issue, but the articles he cites do not support the notion that a person of ordinary skill in the art would accept without question that the claimed olive-derived phenolic compounds would have the claimed therapeutic effects.

Next, CreAgri argues that one with ordinary skill in the art would nevertheless have "knowledge of the *possible* anti-inflammatory effects of olive polyphenols" and would therefore "recognize the significant benefit of the claimed inventions." Pl. Opp. at 22 (emphasis added). The undisputed record does show that, prior to the time of filing, some amount of investigation had been performed into the possible anti-inflammatory effects of olive mill wastewater and of olive-derived phenols. In particular, CreAgri points to five scientific articles cited in the patent specification as demonstrative of what was known in the art, *Id*. at 17, and Pinnaclife concedes that three of these references are reflective of research in the field, Def. MSJ at 21. These are the same references considered above in the written description section, and CreAgri reiterates the same arguments with respect to written description and enablement. The Court rejects CreAgri's arguments here as well, finding that, based on the references cited in the specification, a person of ordinary skill in the art would not accept without question the effectiveness of the claimed therapies in treating the ailments listed in the claims.

In addition, CreAgri submits post-filing articles, authored by the inventor, regarding what CreAgri claims are completed studies based on the proposals disclosed in Example 4 from the specification. *See* Lee Decl. Vol. 3, Ex. 19 ("Manuscript received 11 February 2005. . . . [A]ccepted 21 March 2005"); Ex. 20 ("Received 17 January 2007 . . . accepted 5 June 2007."). CreAgri argues that the Court should consider these results in its enablement analysis as

"pertain[ing] to the accuracy of a statement already in the specification." Pl. Opp. at 22 (quoting *Eli Lilly & Co. v. Actavis Elizabeth LLC*, 435 F. App'x 917, 925 (Fed. Cir. 2011)). However, the Court cannot consider CreAgri's post-filing test results as evidence of the utility of the claimed methods of treating inflammation. "Enablement is determined as of the effective filing date of the patent's application." *In re '318 Patent Infringement Litig.*, 583 F.3d at 1323. Where results "were not available at the time of the application," they cannot be used to establish utility or enablement. *Id.*, 583 F.3d at 1325; *see also* Marshall Decl. Ex. C 175 ("Crea Dep."), ECF No. 103-2 ("[T]he patent was filed while we were doing the study, and the results weren't available.").

The Federal Circuit has created a narrow exception to the rule that post-filing data cannot support utility. In *In re Brana*, 51 F.3d 1560 (Fed. Cir. 1995), the Federal Circuit allowed such evidence "to substantiate any doubts as to the asserted utility" where those test results "pertain[] to the accuracy of a statement already in the specification." *Id.*, 51 F.3d at 1567 n.19. Read too broadly, however, the *Brana* exception would swallow the rule that "[e]nablement, or utility, is determined as of the application filing date." *Id.* Where actual results, garnered post-filing, mirror or otherwise substantiate predicted results, it is plain that those results will pertain to the accuracy of a statement in the specification within the meaning of *Brana*. Here, however, the '599 Patent makes no assertions whatsoever regarding the outcomes of the proposed studies, *see supra* Part III.A.2.b (discussing "Example 4" of the '599 Patent), so the study designs provided in the specification are not sufficiently prophetic such that later-achieved results can support the utility of the claimed invention. *See Brana*, 51 F.3d at 1567 n. 19 (post-filing results "do[] not render an insufficient disclosure enabling, but instead go[] to prove that the disclosure was in fact enabling when filed (i.e., demonstrated utility)").

Moreover, even if it could consider the results at issue, the Court would not conclude that the results create an issue of fact as to whether persons of ordinary skill in the art would accept without question the utility of the claimed treatment as of the filing date of the invention. The first study—a measurement in mice of a marker linked to inflammation called "tumor necrosis factor-α" ("TNF- α ")—explicitly disclaims the anti-inflammatory effects of hydroxytyrosol, both as to the mouse model in question and with regard to other, undisclosed anti-inflammatory cell models. Lee

Decl. Ex. 19 at 1478 ("HT [Hydroxytyrosol] . . . was ineffective at attenuating TNF-α production in this cell system. We evaluated the effectiveness of pure HT in other anti-inflammatory cell models and found that it was also ineffective in those models (unpublished results)."). The study concludes that "although the major phenolic compound of hydrolyzed olive water is [hydroxytyrosol], the anti-inflammatory activity [found in the study] may be attributable to another component of the water that is as yet unidentified." *Id.* Thus, CreAgri's own evidence demonstrates that the effectiveness of hydroxytyrosol as an anti-inflammatory was still uncertain to those of ordinary skill in the art even after the date of filing.

The second study measured the effect of "olive extract supplement" on male and female volunteers suffering from osteoarthritis or Rheumatoid arthritis. Lee Decl. Ex. 20 at 475. Significantly, the arthritis study did not reference relative concentrations of hydroxytyrosol to oleuropein, or, indeed, even mention either substance. *See Id*. Further, given that the study only measures the effects of the "olive extract supplement" on Rheumatoid arthritis and osteoarthritis, even a study finding that the supplement was successful in 100% of cases could not enable the full scope of the '599 Patent's claims, as the claims recite treating coronary, bronchial, and neuro inflammation (claim 1), and inflammation from psoriasis, organ transplant, fever, and tissue graft rejection (claim 16). As CreAgri highlights, this study was generally a success, finding a statistically significant reduction in several of the subjects' inflammation symptoms over the placebo group. *Id*. at 473–76. It is possible that, as to claims to an olive extract supplement treatment for Rheumatoid arthritis and osteoarthritis, this study could form the basis of an enabling disclosure. However, these are not the claims at issue. As discussed above, even if this data was available at the time the patent was filed, the arthritis study cannot enable any of the '599 Patent's claims, as it does not mention hydroxytyrosol or oleuropein. And, even if the data was available pre-filing, and even assuming that the "olive extract supplement" in the study was a supplement with the claimed ratios of hydroxytyrosol to oleuropein, the arthritis study still cannot enable the full scope of the '599 Patent's claims because it only deals with the treatment of arthritis, without mentioning any of the other claimed ailments.

In sum, Pinnaclife has satisfied its burden of establishing that no reasonable jury could conclude that a person of ordinary skill in the art would accept without question the general assertion that olive-derived phenols would effectively treat the various forms of inflammation as recited in the claims. The '599 Patent's claims are not enabled on this basis.

b. The specification and the prior art references do not otherwise establish utility

Although the operability of a patented therapy need not be demonstrated by testing in order to satisfy the utility and enablement requirements, if the claimed effect would not otherwise be accepted by one of ordinary skill in the art, there must nevertheless be some quantum of data or reasoning that supports the inventor's contention that a therapy operates as claimed. *See In re '318 Patent Infringement Litig.*, 583 F.3d at 1326. The PTO's Manual of Patent Examining Procedure ("MPEP")[18] provides that "[a]s a general matter, evidence of pharmacological or other biological activity of a compound will be relevant to an asserted therapeutic use if there is a *reasonable correlation* between the activity in question and the asserted utility." MPEP § 2107.03 (emphasis added). Such a correlation may be demonstrated by "statistically relevant data documenting the activity of a compound or composition, arguments or reasoning, documentary evidence (*e.g.*, articles in scientific journals), or any combination thereof." *Id.*; *see also Cross v. Iizuka*, 753 F.2d 1040, 1050 (Fed. Cir. 1985) (finding a "reasonable correlation" between *in vitro* results and purported *in vivo* utility of a pharmaceutical).

As the Federal Circuit noted in *In re '318 Patent Infringement Litig.*, circumstances where analytic reasoning alone will demonstrate utility are likely to be rare, *see* 583 F.3d at 1326, and CreAgri points to no precedent in which such evidence was sufficient to satisfy utility and enablement.[19] In *In re '318 Patent Infringement Litig.*, the Federal Circuit upheld a ruling of

[18] "The MPEP . . . [is] not binding on this court, but may be given judicial notice to the extent [it does] not conflict with the statute." *In re Fisher*, 421 F.3d 1365, 1372 (Fed. Cir. 2005) (internal quotation marks omitted).

[19] CreAgri looks to *Brana* and *Actavis* to support the utility of the '599 Patent. *See* Pl. Opp. at 21–22. Neither case involved facts comparable to those at bar. In *Brana*, the Federal Circuit found that there was sufficient evidence of utility for chemical compounds intended for use as antitumor substances where the patentee disclosed *in vitro* results of the claimed compound's effectiveness and where the claimed compound was structurally similar to a compound proven to be effective *in vivo*. *See* 51 F.3d at 1563, 1567. In *Actavis*, the FDA had authorized using the compound at issue for the claimed treatment in human clinical trials, which, the court highlighted, already required the

invalidity concerning a patent for a method of treating Alzheimer's disease where the specification grounded the compound's efficacy on its other known effects as described in the scientific literature and made no reference to either *in vitro* or *in vivo* testing. *See In re '318 Patent Infringement Litig.*, 583 F.3d 1321–22. While the Court did not rule out the possibility of disclosing utility through "analytic reasoning" based on known properties, it found that any analytic insights made by the inventor were "nowhere described in the specification," and therefore did not need to reach the question of whether such insights were sufficient. *Id.* at 1326. Accordingly, although a patentee need not generally know "how or why the invention works," *In re Cortright*, 165 F.3d 1353, 1359 (Fed. Cir. 1999) (internal quotation marks omitted), such explanations do become necessary where, as here, the inventor did not know at the time of filing whether the invention was in fact operable and instead rests the invention's asserted operability on, as the inventor himself conceded, "prophe[cy]." *See* Crea Dep. at 174:7–23.

Here, as in *In re '318 Patent Infringement Litig.*, the specification provides nothing that could be considered argument or analytic reasoning. The '599 Patent specification, at ten pages long, is at the very least more lengthy than that of the patent invalidated by *In re '318 Patent Infringement Litig*. *See In re '318 Patent Infringement Litig.*, 583 F.3d at 1321 ("The specification . . . was only just over one page in length"). It is not, however, any more revealing as to the claimed therapy. Although the specification presents various means of *testing* whether the claimed invention would work as to a small subset of the recited causes of inflammation, *see* '599 Patent at cols. 10–13, 16–19, it does not explicitly provide any analytic reasoning as to why the invention would work as claimed.

The '599 Patent does not claim a therapy, it claims a research hypothesis. "[R]esearch hypotheses do not qualify for patent protection." *Ariad*, 598 F.3d at 1353. Because a reasonable

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applicant to "provide a convincing rationale to those especially skilled in the art (*e.g.*, the [FDA]) that the investigation may be successful." 435 F. App'x at 924 (internal quotation marks omitted). Moreover, the compound at issue in *Actavis* was known to have the same relevant biological activity exhibited by another drug used to treat the same condition named in the patent, even though the other drug's safety was questioned. *Id.* at 920, 926. Here, CreAgri has not disclosed *in vivo* "evidence of success in structurally similar compounds," *Brana*, 51 F.3d at 1567, or any suggestion that the FDA has approved human trials of the claimed or similar substances.

jury could not conclude that a person of ordinary skill in the art reading the patent at the time of filing would recognize the utility of the full scope of the claimed therapies, the claims are not enabled and are therefore invalid pursuant to sections 101 and 112. The Court therefore grants Pinnaclife's Motion for Summary Judgment on invalidity as to the '599 Patent.

C. Whether the '599 Patent is invalid as indefinite under 35 U.S.C. § 112(b)

Pinnaclife has also moved for summary judgment of invalidity on the grounds that the '599 Patent is invalid as indefinite under 35 U.S.C. § 112(b). As all claims of the '599 Patent are invalid for failure to meet the written description and enablement requirements of subsection 112(a), the Court declines to address the parties' arguments as to indefiniteness.

V. CONCLUSION

For the foregoing reasons, the Court GRANTS Pinnaclife's Motion for Summary Judgment of Invalidity in its entirety. Because CreAgri asserts no patents beyond those the Court now rules invalid, the Court DENIES as moot CreAgri's Motion for Summary Judgment of Infringement. Moreover, as CreAgri's only causes of action seek to enforce patents the Court now rules invalid in their entirety, the case is hereby DISMISSED. Accordingly, the Court dismisses Pinnaclife's first Counterclaim for a Declaratory Judgment of Noninfringement of the '808 and '599 Patents and second Counterclaim for a Declaratory Judgment of Unenforceability of the '808 Patent without prejudice.[20] All other outstanding motions besides the administrative motions to seal and the motion to disqualify Dr. Visioli are DENIED as moot.[21]

[20] The Federal Circuit has held that a summary judgment grant of noninfringement does not moot a counterclaim for invalidity. *Liquid Dynamics Corp. v. Vaughan Co.*, 355 F.3d 1361, 1370 (Fed. Cir. 2004). The Federal Circuit has held similarly with respect to a counterclaim for unenforceability. *Zenith Elects. Corp. v. PDI Commc'n Sys., Inc.*, 522 F.3d 1348, 1366–67 (Fed. Cir. 2008). Rather than moot the claim, the Federal Circuit has instructed district courts to either hear the claim or dismiss it without prejudice. *Liquid Dynamics*, 355 F.3d at 1371 ("A district court judge faced with an invalidity counterclaim challenging a patent that it concludes was not infringed may either hear the claim or dismiss it without prejudice, subject to review only for abuse of discretion."); *see also Korszun v. Pub. Techs. Multimedia, Inc.*, 96 F. App'x 699, 700 (Fed. Cir. 2004) ("(1) the district court can proceed to trial on the invalidity counterclaims and adjudicate them to finality, thus 'end[ing] the litigation on the merits and leav[ing] nothing for the court to do but execute the judgment[,];' . . . (2) the district court can dismiss the counterclaims; (3) the district court can, where proper, enter judgment under Federal Rule of Civil Procedure 54(b); and (4) the procedures of 28 U.S.C. § 1292(b), (c)(1) can be invoked." (quoting *Nystrom v. TREX Co.*, 339 F.3d 1347, 1350–51 (Fed. Cir. 2003)) (citation omitted)). Here, the Court is faced with the reverse situation of a grant of summary judgment on invalidity with outstanding counterclaims for

IT IS SO ORDERED.

Dated: December 18, 2013

LUCY H. KOH
United States District Judge

United States District Court
For the Northern District of California

noninfringement and unenforceability. To ensure that the Federal Circuit will have proper jurisdiction for an appeal of this decision, and out of an abundance of caution, the Court dismisses the counterclaims without prejudice rather than as moot. *See Nystrom*, 339 F.3d at 1350–51 (Fed. Cir. 2003).

[21] The parties have filed various administrative motions to seal. The Court will address those motions in a separate order.

UNITED STATES DISTRICT COURT

NORTHERN DISTRICT OF CALIFORNIA

SAN JOSE DIVISION

CREAGRI, INC., a California Corporation, Plaintiff, v. PINNACLIFE INC., a Nevada Corporation, Defendant.	Case No.: 11-CV-06635-LHK ORDER CONSTRUING DISPUTED CLAIM TERMS OF U.S. PATENT NOS. 6,416,808 and 8,216,599

Plaintiff CreAgri, Inc. ("CreAgri") brings this action for patent infringement against Defendant Pinnaclife Inc. ("Pinnaclife"). The parties now seek construction of four disputed terms used in the claims of the following patents-in-suit: U.S. Patent Nos. 6,416,808 ("'808 Patent") and 8,216,599 ("'599 Patent"). The Court held a technology tutorial and a claim construction hearing on February 8, 2013. The Court has reviewed the claims, specifications, and other relevant evidence, and has considered the briefing and arguments of the parties at the February 8, 2013 claim construction hearing. The Court now construes the terms at issue.

I. BACKGROUND

A. Background and Description of the Invention

The two patents-in-suit generally relate to compounds obtained from olive plants. At the time of the invention, olives were known to contain compounds, that, when ingested, provide

beneficial health effects. *See* '808 Patent at 2:9-30. Those health effects were attributed to phenolic compounds, in particular, hydroxytyrosol and oleuropein. *See id.* Both hydroxytyrosol and oleuropein are present in the water byproduct obtained from industrial olive oil production, which is known as "vegetation water." *See* '808 Patent at 2:41-49. Tyrosol, another phenolic compound, also exists in vegetation water but is an undesired component. '808 Patent at 4:43-46.

The '808 Patent, entitled "Method of Obtaining a Hydroxytyrosol-rich Composition From Vegetation Water," is directed to olive-derived dietary supplements that contain hydroxytyrosol and oleuropein or hydroxytyrosol and tyrosol at certain weight ratios. *See* '808 Patent at 3:43-51. The patent specification also discloses methods for producing hydroxytyrosol-rich compositions from olives, which involves converting oleuropein present in the vegetation water to hydroxytyrosol under appropriate conditions. *See* '808 Patent at 2:57-67. However, no claim is directed towards these methods.[1] The '599 Patent, entitled "Method for Treatment of Inflammation," discloses methods for treating certain inflammation conditions, with a treatment agent containing substantially purified hydroxytyrosol or a substantially purified mixture of hydroxytyrosol and oleuropein. *See* '599 Patent Abstract.

CreAgri alleges that a number of Pinnaclife's products infringe the '808 Patent and the '599 Patent. ECF No. 50 ("Second Amended Complaint" or "SAC"), ¶¶ 51-77. In addition, CreAgri accuses Pinnaclife of actively inducing infringement of the '599 Patent. SAC, ¶ 60.

B. Claim Terms at Issue

In the parties' Joint Claim Construction Statement, the parties identified ten claim terms to be construed:

1. "comprising" or "comprised of";
2. "aqueous extract of olives";
3. "olive plant extract"

[1] The '808 Patent Application initially included 16 claims directed towards methods producing hydroxytyrosol-rich compositions from olives ("Method Claims"). *See* CreAgri's Opening Claim Construction Brief, Exs. 6 and 7. These claims were removed from the '808 Patent during prosecution pursuant to a restriction requirement. *See id.*, Ex. 7; Pinnaclife's Resp., Ex. D. Many of these claims (or claims similar to them) were ultimately included in a divisional of the '808 Patent, *see* U.S. Patent Nos. 7,261,909, and a continuation-in-part of the '808 Patent, *see* U.S. Patent No. 7,713,569.

4. "about"
5. "powder extract"
6. "inflammatory condition"
7. "clinical symptom" or "detectable clinical symptom";
8. "marker" or "biochemical marker";
9. "first treatment agent"
10. "second disease treatment agent" or "second treatment agent"

See ECF No. 43 ("Joint Claim Construction Statement").

In the Joint Claim Construction Statement, the parties also identified two additional terms upon whose construction the parties agree.

Claim Language	Construction
"substantially purified" and "substantially purified mixture"	"a compound or compounds that are removed from their natural environment, isolated or separated, and are at least 60% free from other components with which they are naturally associated"
"coincident"	plain and ordinary meaning.

Id. at 1-2. The Court adopts the parties' construction of these terms.

Additionally, in the course of claim construction briefing, CreAgri and Pinnaclife agreed upon the construction of the following terms:

Claim Language	Construction
"about"	plain and ordinary meaning
"powder extract"	plain and ordinary meaning
"inflammatory condition"	plain and ordinary meaning
"first treatment agent"	plain and ordinary meaning
"olive plant extract"	"a preparation from an olive plant"
"second disease treatment agent" and "second treatment agent"	"a compound administered in addition to the first disease treatment agent of claim 1, where the compound acts to treat coronary, bronchial or neuro inflammation"

See Pinnaclife's Responsive Claim Construction Br. at 5-6 ("Pinnaclife's Resp.") (adopting CreAgri's proposed definitions of "about," "powder extract," "inflammatory condition," "first

treatment agent," and "olive plant extract"); CreAgri's Reply Claim Construction Brief ("CreAgri's Reply") at 15 (adopting Pinnaclife's definitions of "second disease treatment agent" and "second treatment agent"). The Court adopts the parties' construction of the aforementioned terms.

In Pinnaclife's Responsive Brief, Pinnaclife states that, during the parties' meet and confer process, Pinnaclife identified the following terms, which appear "in at least [C]laim 1 of the '599 [P]atent[,] as insolubly ambiguous and therefore indefinite: 'normal range,' 'desired change,' 'elevated levels,' and 'respiratory distress.'" Pinnaclife's Resp. at 6. Pinnaclife states that CreAgri has offered no construction for these terms. *Id.* Accordingly, Pinnaclife states that, if necessary, Pinnaclife will seek summary judgment of invalidity under 35 U.S.C. § 112 ¶ 2 consistent with the Court's scheduling order. *Id.* CreAgri responds that its position is, and has always been, that the aforementioned terms require no construction because the plain and ordinary meaning applies. *See* CreAgri's Reply at 2. CreAgri notes that it stated as much in its preliminary claim construction chart. *See* Declaration of Harold Storey in Support of Plaintiff CreAgri, Inc.'s Reply, ECF No. 52, Ex. 1 at 5. Because the challenged terms were not identified as requiring construction in the parties' Joint Claim Construction Statement, and the parties have not briefed the issue of whether these terms are insolubly ambiguous, the Court will not address them at this time.

Thus, the terms requiring construction by the Court are as follows:

1. "comprising" or "comprised of";
2. "aqueous extract of olives";
3. "clinical symptom" or "detectable clinical symptom";
4. "marker" or "biochemical marker."

Additionally, ostensibly in the context of construing the terms "comprising" or "comprised of," Pinnaclife raised three additional construction issues:

1. whether the preamble "a dietary supplement" sets forth a limitation;
2. whether the weight ratios of hydroxytyrosol and oleuropein and hydroxytyrsol and tyrosol described in Claims 1 and 5 of the '808 Patent, respectively, apply to the "dietary supplement" or to the "aqueous extract" referenced in those claims; and

3. whether the the weight ratio of hydroxytyrosol and oleuropein described in Claim 1 of the '599 Patent apply to the "first treatment agent" or "olive plant extract" referenced in that claim.

See Joint Claim Construction Statement at 3; Pinnaclife's Resp. at 8-14.

While the Court does not agree with the parties that these construction issues are relevant to the proper construction of the terms "comprising" or "comprised of," the Court will address these issues as well.

II. LEGAL STANDARD

Claim construction is a question of law to be determined by the court. *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 979 (Fed. Cir. 1995) (en banc), *aff'd* 517 U.S. 370 (1996). "Ultimately, the interpretation to be given a term can only be determined and confirmed with a full understanding of what the inventors actually invented and intended to envelop with the claim." *Phillips v. AWH Corp.*, 415 F.3d 1303, 1316 (Fed. Cir. 2005) (en banc) (internal quotation marks omitted). Accordingly, a claim should be construed in a manner that "stays true to the claim language and most naturally aligns with the patent's description of the invention." *Id.*

In construing disputed terms, the court looks first to the claims themselves, for "[i]t is a 'bedrock principle' of patent law that 'the claims of a patent define the invention to which the patentee is entitled the right to exclude.'" *Id*. at 1312 (quoting *Innova/Pure Water, Inc. v. Safari Water Filtration Sys., Inc.*, 381 F.3d 1111, 1115 (Fed. Cir. 2004)). Generally, the words of a claim should be given their "ordinary and customary meaning," which is "the meaning that the term[s] would have to a person of ordinary skill in the art in question at the time of the invention." *Id.* at 1312-13. In some instances, the ordinary meaning to a person of skill in the art is clear, and claim construction may involve "little more than the application of the widely accepted meaning of commonly understood words." *Id.* at 1314.

In many cases, however, the meaning of a term to a person skilled in the art will not be readily apparent, and the court must look to other sources to determine the term's meaning. *Id.* Under these circumstances, the court should consider the context in which the term is used in an asserted claim or in related claims, bearing in mind that "the person of ordinary skill in the art is

deemed to read the claim term not only in the context of the particular claim in which the disputed term appears, but in the context of the entire patent, including the specification." *Id.* at 1313. Indeed, the specification is "'always highly relevant'" and "'[u]sually [] dispositive; it is the single best guide to the meaning of a disputed term.'" *Id.* at 1315 (quoting *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996)). Where the specification reveals that the patentee has given a special definition to a claim term that differs from the meaning it would ordinarily possess, "the inventor's lexicography governs." *Id.* at 1316. Likewise, where the specification reveals an intentional disclaimer or disavowal of claim scope by the inventor, the inventor's intention as revealed through the specification is dispositive. *Id.*

A court may also consider the patent's prosecution history, which consists of the complete record of proceedings before the United States Patent and Trademark Office ("U.S. PTO" or "PTO") and includes the cited prior art references. A court may consider prosecution history where it is in evidence, for the prosecution history "can often inform the meaning of the claim language by demonstrating how the inventor understood the invention and whether the inventor limited the invention in the course of prosecution, making the claim scope narrower than it otherwise would be." *Id.* at 1317 (internal citations omitted).

Finally, a court is also authorized to consider extrinsic evidence in construing claims, such as "expert and inventor testimony, dictionaries, and learned treatises." *Markman*, 52 F.3d at 980 (internal citations omitted). Expert testimony may be particularly useful in "[providing] background on the technology at issue, [explaining] how an invention works, [ensuring] that the court's understanding of the technical aspects of the patent is consistent with that of a person of skill in the art, or [establishing] that a particular term in the patent or the prior art has a particular meaning in the pertinent field." *Phillips*, 415 F.3d at 1318. Although a court may consider evidence extrinsic to the patent and prosecution history, such evidence is considered "less significant than the intrinsic record" and "less reliable than the patent and its prosecution history in determining how to read claim terms." *Id.* at 1317-18 (internal quotation marks and citation omitted). Thus, while extrinsic evidence may be useful in claim construction, ultimately "it is unlikely to result in a reliable interpretation of patent claim scope unless considered in the context

of the intrinsic evidence." *Id.* at 1319. Any expert testimony "that is clearly at odds with the claim construction mandated by the claims themselves, the written description, and the prosecution history" will be significantly discounted. *Id.* at 1318 (internal quotation marks and citation omitted).

III. DISCUSSION

A. "comprising" or "comprised of"

Terms in Dispute	CreAgri's Proposed Construction	Pinnaclife's Proposed Construction
"comprising" or "comprised of"	"including but not limited to"	**'808 Patent**: "containing as part of the dietary supplement" **'599 Patent**: "containing as part of the treatment agent administered to a subject having an inflammatory condition"

The term "comprising" appears in independent Claims 1 and 5 of the '808 Patent, as follows:

> 1. A dietary supplement **comprising** an aqueous extract of olives containing a weight ratio of hydroxytyrosol to oleuropein of between about 5:1 and about 200:1.
> 5. A dietary supplement **comprising** an aqueous extract of olives containing a weight ratio of hydroxytyrosol and tyrosol of between about 3:1 and about 50:1.

'808 Patent at 10:36-38, 10:48-50 (emphasis added).

The term "comprised of" appears in Claim 1 of the '599 Patent, as follows:

> 1. A method of treating a subject having an inflammatory condition characterized by a detectable clinical symptom or change in a level of a biochemical marker with respect to the normal range of the marker, the method comprising:
>
> administering to the subject a dose corresponding to between about 0.1 mg/kg body weight and 2000 mg/kg body weight daily of a first treatment agent **comprised of** an olive plant extract having a weight ratio of hydroxytyrosol to oleuropein of between about 1:1 and about 200:1; and
>
> continuing said administration until there is observed a return of the marker level to the normal range or a desired change in the clinical symptom,
>
> where the marker or the clinical symptom is selected from the group consisting of:
>
> (i) elevated levels of C-reactive protein in the case of coronary inflammation;
>
> (ii) respiratory distress in the case of bronchial inflammation; and

> (iii) elevated CSF levels of isoprostanes or clinical symptoms determined from neuropsychological testing in the case of neuro inflammation.

'599 Patent at 19:37-20:5 (emphasis added).[2]

CreAgri argues that "comprising" and "comprised of" should be construed as permitting additional elements, and that, as a result, the terms should be construed as meaning "including but not limited to." CreAgri's Opening Claim Construction Brief ("CreAgri's Opening Br.") at 6. Notwithstanding the difference in the proposed language, Pinnaclife does not dispute that the term "comprising… allows for incorporation of additional elements not expressly identified in the claim." *See* Pinnaclife's Resp. at 7. Indeed, at the *Markman* hearing, both parties agreed to construe "comprising" and "comprised of" as "including but not limited to." *See* ECF No. 62 (Transcript of the February 8, 2013 *Markman* Hearing) ("Tr.") at 37:20-24, 38:16-20. This construction is consistent with how the Federal Circuit has construed these terms. *See, e.g.*, *CIAS, Inc. v. Alliance Gaming Corp.*, 504 F.3d 1356, 1360 (Fed. Cir. 2007) ("In the patent claim context the term 'comprising' is well understood to mean 'including but not limited to.'" "The usual and generally consistent meaning of 'comprised of,' when it is used as a transition phrase, is, like 'comprising,' that the ensuing elements or steps are not limiting."); *see also* Manual of Patent Examining Procedure ("MPEP") § 2111.03 ("The transitional term 'comprising'…is inclusive or open-ended and does not exclude additional, unrecited elements or method steps."). Accordingly, the Court adopts CreAgri's construction and construes "comprising" and "comprised of" as "including but not limited to."

Pinnaclife raises two additional arguments in the context of construing "comprising" and "comprised of." First, Pinnaclife argues that the use of "dietary supplement" in the preambles of independent Claims 1 and 5 imposes a limitation on the '808 Patent. *See* Pinnaclife's Resp. at 8. Second, Pinnaclife argues that the weight ratios disclosed in Claims 1 and 5 of the '808 Patent and

[2] In the Joint Claim Construction Statement, Pinnaclife also proposed a construction for the term "comprising" as used in Claim 16 of the '599 Patent. *See* ECF No. 43 at 3. This construction appears to have been abandoned in Pinnaclife's claim construction briefing. *See* Pinnaclife's Resp. at 6-7. At the *Markman* hearing, Pinnaclife confirmed that it no longer disputes the meaning of "comprising" as used in Claim 16 of the '599 Patent. *See* Tr. at 14:18-24. Accordingly, the Court only construes "comprising" or "comprised of" as used in Claims 1 and 5 of the '808 Patent, and in Claim 1 of the '599 Patent.

Claim 1 of the '599 Patent apply to the "dietary supplement" and "treatment agent" respectively. *See id.* at 12. The Court is not persuaded that these issues are related to the construction of "comprising" and "comprised of." At the *Markman* hearing, Pinnaclife agreed that the issues relating to the preamble and weight ratios did not necessarily need to be resolved in the context of construing "comprising" and "comprised of," so long as these issues are addressed. *See* Tr. 102:21-103:21. Therefore, the Court addresses these two issues below in separate sections.

B. The Preamble "a dietary supplement"

Term in Dispute	CreAgri's Proposed Construction	Pinnaclife's Proposed Construction
The preamble "a dietary supplement"	The preamble "a dietary supplement" is not a claim limitation.	The preamble "a dietary supplement" limits all claims of the '808 Patent.

"A dietary supplement" is used as preambles in independent Claims 1 and 5 of the '808 Patent, as follows:

> 1. **A dietary supplement** comprising an aqueous extract of olives containing a weight ratio of hydroxytyrosol to oleuropein of between about 5:1 and about 200:1.
>
> 5. **A dietary supplement** comprising an aqueous extract of olives containing a weight ratio of hydroxytyrosol and tyrosol of between about 3:1 and about 50:1.

'808 Patent at 10:36-38, 10:48-50 (emphasis added).

Pinnaclife argues that the preamble "a dietary supplement" imposes a limitation on all claims of the '808 Patent. *See* Pinnaclife's Resp. at 8. CreAgri, on the other hand, contends that "a dietary supplement" does not establish a limitation. *See* CreAgri's Reply Br. at 5-6.

As an initial matter, the Court notes with disapproval that Pinnaclife did not raise its argument that the preamble is a claim limitation or disclose the evidence upon which it intended to rely in the Joint Claim Construction Statement. Nevertheless, the Court believes that CreAgri was able to adequately respond to Pinnaclife's arguments in CreAgri's Reply and at the *Markman* hearing. Thus, the Court will address this issue on the merits.

In general, a preamble limits the invention if it recites essential structure or steps, or if it is "necessary to give life, meaning, and vitality" to the claim. *Catalina Mktg. Int'l, Inc. v. Coolsavings.com, Inc.*, 289 F.3d 801, 808 (Fed. Cir. 2002). Conversely, a preamble is not limiting

"where a patentee defines a structurally complete invention in the claim body and uses the preamble only to state a purpose or intended use for the invention." *Id.* While there is no litmus test for determining when a preamble operates as a limitation, courts have provided certain "guideposts" or examples of circumstances in which a preamble may establish a claim limitation. These circumstances include when: (1) the "Jepson" form is used for a claim[3]; (2) the preamble is "essential to understand the limitations or terms in the claim body" (*e.g.* when a preamble phrase provides the antecedent basis for other terms in the claim body); (3) the preamble recites "additional structure or steps underscored as important by the specification"; and (4) a patentee clearly relies on the preamble during prosecution to distinguish the claimed invention from the prior art. *Id.*

Here, Pinnaclife makes several arguments regarding why the preamble "a dietary supplement" should be construed as limiting. First, citing *Catalina*, Pinnaclife argues that the preamble is limiting because it is "essential to understand the… terms in the… body" of dependent Claim 3. *See* Pinnaclife's Resp. at 9 (quoting *Catalina*, 289 F.3d at 808). Pinnaclife also argues that its proposed construction is supported by the specification. *See id.* Finally, Pinnaclife makes several arguments relating to the prosecution history. *See id.* at 9-11. The Court will address the claim language, specification, and prosecution history in turn.

1. Claim Language

First, Pinnaclife argues that the preamble of independent Claims 1 and 5 should be construed as limiting because dependent Claim 3 "incorporates the preamble into" the body of Claim 3. *See id.* at 9. Dependent Claim 3 states: "The dietary supplement of [C]laim 1, wherein *said supplement* is dried to provide a powder extract." '808 Patent at 10:42-43 (emphasis added). Pinnaclife argues that the reference to "supplement" in Claim 3 "may only be understood with reference to the 'dietary supplement' preamble." *See id.* at 9. Thus, Pinnaclife argues that because

[3] "A Jepson claim is to an improvement on an existing device, process[,] or combination, and includes (1) a preamble reciting conventional elements or steps, (2) a transition phrase such as 'wherein the improvement comprises,' and (3) the elements or steps the applicant considers to be new." DONALD S. CHISUM ET AL., UNDERSTANDING INTELLECTUAL PROPERTY LAW 116 (2nd ed. 2011); *see also* 37 C.F.R. § 1.75(e). Here, neither Claim 1 nor Claim 5 claims an improvement on an existing device, process, or combination. Thus, neither claim is a Jepson claim.

the preamble is "essential to understand the limitations or terms in the body" of Claim 3, it is limiting. *See id.* (quoting *Catalina*, 289 F.3d at 808). The Court is not persuaded by this argument.

Catalina did indeed recognize that a preamble may be limiting where the preamble provides the antecedent basis for a term in the claim body, such that the preamble is "essential to understand the limitations or term in the body." *See Catalina*, 289 F.3d at 808. Applying this principle, the *Catalina* Court found that the phrase "located at predesignated sites such as consumer stores" limited independent Claim 25. *See id.* at 810-11. Claim 25 provided for: "A system for controlling the selection and dispensing of product coupons at a plurality of remote terminals *located at predesignated sites such as consumer stores*, comprising: a plurality of free standing coupon display terminals *located at predesignated sites such as consumer stores*, each of said terminals being adapted for bidirectional data communication with a host central processing unit…." *Id.* at 806. The *Catalina* Court reasoned that because the phrase "located at predesignated sites such as consumer stores" appeared in both "the preamble and [the] body of" that claim, the preamble established a limitation. *See id.* at 810-11.

In the present case, the preamble "a dietary supplement" does not appear in the bodies of Claims 1 and 5. Indeed, Claims 1 and 5 of the '808 Patent "define[]… structurally complete invention[s]." *Id.* at 808. Specifically, Claims 1 and 5 describe compositions comprised of aqueous extracts with certain ratios of hydroxytyrosol and oleuropein or hydroxytyrosol and tyrosol, respectively. The preamble phrase "a dietary supplement" does not provide any additional information about the structure of the compositions (*i.e.* its chemical components and their relative ratios). Accordingly, removing the preamble phrase would "not affect the structure" of the claimed compositions. *Id.* at 809 ("[T]he preamble generally is not limiting when the claim body describes a structurally complete invention such that deletion of the preamble phrase does not affect the structure or steps of the claimed invention."). Thus, with respect to Claims 1 and 5, it appears that "the preamble only… state[s] a purpose or intended use for the invention." *Id.* at 808. As set forth in *Catalinia*, "preambles describing the use of an invention generally do not limit the claims because the patentability of apparatus or composition claims depends on the claimed structure, not on the use or purpose of that structure." *Id.* at 809.

Pinnaclife argues that the preamble "a dietary supplement" should, nevertheless, be construed as limiting because it appears in the preamble and the body of dependent Claim 3. *See* Pinnaclife Resp. at 9. However, Pinnaclife fails to cite, and the Court is unaware of, any authority for the proposition that a preamble phrase appearing in an independent claim should be construed as limiting that independent claim simply because that phrase appears in both the preamble and the body of a dependent claim. *Catalina* did not address this issue as the *Catalina* Court considered only whether the preamble found in independent Claim 25 was limiting where it appeared in both the preamble and the body of *that* claim. Thus, the Court is not persuaded that the preamble "a dietary supplement" should be construed as limiting Claims 1 and 5 (or the Patent as a whole) simply because it appears in the preamble and the body of dependent Claim 3. The claim language therefore does not support Pinnaclife's argument that the preamble is limiting. Furthermore, as well be discussed below, the specification confirms that compositions claimed in the '808 Patent were not intended to be limited to uses as dietary supplements.[4]

2. Specification

Pinnaclife also argues that several elements of the specification support Pinnaclife's construction that the preamble is limiting. *See* Pinnaclife's Resp. at 9. As explained in *Catalina*, a preamble may be limiting where it recites "additional structure or steps underscored as important by the specification." *Catalina*, 289 F.3d at 808. Here, Pinnaclife argues that "dietary supplement" should be construed as limiting because the Abstract states that: "The invention provides an olive-derived *dietary supplement* comprising hydroxytyrosol and oleuropein in specific weight ratios." '808 Patent Abstract. Similarly, the Summary of the Invention states that "the invention includes a dietary supplement." *Id.* at 3:43-54. Finally, Pinnaclife notes that the section

[4] Pinnaclife also argues that Dependent Claims 2 and 6 "do not stand as complete inventions without reading 'supplement' or 'dietary supplement' as part of the claim." Pinnaclife's Resp. at 9. Pinnaclife argues that this supports the conclusion that the preamble in Claim 1 is limiting. *See id.* Even accepting *arguendo* that Claims 2 and 6 did not "stand as complete inventions without reading 'supplement' or dietary supplement' as part of the claim," *id.*, Pinnaclife fails to cite any authority for the proposition that a preamble phrase contained in an independent claim limits the independent claim if a dependent claim cannot "stand as a complete invention[]" without referencing the preamble phrase.

disclosing the composition is titled "Hydroxytyrosol-Rich *Dietary Supplement*." *id.* at 7:28 (emphasis added).

The Court finds these references to the specification unpersuasive. None of the references "underscore[s]" that the dietary supplement use of the composition is an important part of the composition's structure. *Catalina*, 289 F.3d at 808. The statement in the Abstract describes the composition as being "compris[ed] [of] hydroxytyrosol and oleuropein in specific weight ratios." '808 Patent Abstract. Like Claims 1 and 5 (discussed *supra*), the reference to a "dietary supplement" in the first portion of the Abstract sentence describes a possible use of the composition. *Id*. Similarly, the statement in the Summary of the Invention that "the invention includes a dietary supplement" does not clearly indicate that the composition's use was meant to be limited to dietary supplements. *Id.* at 3:43-54 (emphasis).

Finally, and most significantly, the first sentence in the portion of the specification titled "Hydroxytyrosol-Rich Dietary Supplement" explicitly states that use as a dietary supplement is but one possible use for the invention: "III. Hydroxytrosol-Rich Dietary Supplement. It should be appreciated that hydroxytrosol produced by the method described above may be used for a *variety* of applications. For example…: (i) as a natural anti-bacterial, anti-viral and/or fungicidal product for agricultural and/or pest control applications, and (ii) as a therapeutic and/or an anti-oxidant for a variety of health purposes." *See* '808 Patent at 7:30-38 (emphasis added). Thus, rather than supporting Pinnaclife's construction, the specification supports CreAgri's position that the invention is not limited to use as a dietary supplement. The Court next addresses Pinnaclife's arguments regarding the prosecution history.

3. Prosecution History

Pinnaclife argues that the prosecution history supports its argument that the preamble should be limiting. Indeed, a preamble may be limiting where the inventor has "clear[ly] reli[ed] on the preamble during prosecution to distinguish the claimed invention from the prior art." *Catalina*, 289 F.3d at 808. Pinnaclife makes three arguments relating to the prosecution history. None of these arguments is persuasive. The Court addresses each argument in turn.

With respect to the prosecution history, Pinnaclife first argues that in describing the Reasons for Allowance, the Examiner stated: "WO 00/36936, is cited to show further the state of the art with respect to *dietary supplement compositions* comprising aqueous extracts of tyrosol and hydroxytyrosol." Marshall Decl., Ex. E at 2 (emphasis added). Pinnaclife argues that this statement indicates that the Patent Examiner considered prior art relating to dietary supplements in granting the '808 Patent. Pinnaclife's Resp. at 11. The Court disagrees. While the Reasons for Allowance indicate that the Patent Examiner considered other dietary supplements in granting the '808 Patent, in the same document, the examiner explicitly states that the '808 Patent was granted because it claimed unique mixtures of hydroxytyrosol to oleuropein or hydroxytyrosol to tyrosol. *See* Marshal Decl., Ex. E (stating that the claim was allowed because "[n]one of the prior art references teaches or suggests the weight ratios of hydroxytyrosol to oleuropein or hydroxytyrosol to tyrosol as are instantly claimed"). Thus, the examiners' Reasons for Allowance fail to demonstrate that the dietary supplement use of the product was essential in distinguishing the invention from the prior art such that it may be inferred that CreAgri "clear[ly] reli[ed]" on the supplement's dietary use in order to obtain its patent. *Catalina*, 289 F.3d at 808.

Pinnaclife's second prosecution history related argument concerns the patent Abstract. Pinnaclife notes that the portion of the Abstract reading "The invention provides olive-derived hydroxytyrosol" was changed to "The invention provides *an* olive-derived *dietary supplement comprising* hydroxytyrosol *and* oleuropein *in specific weight ratios*." *See* Storey Decl., Ex. 7 at 18 (the emphasized terms represent the additions). Furthermore, the Abstract was revised to eliminate certain language referring to certain non-dietary uses of the claimed invention including "as a natural anti-bacterial, anti-viral[,] and fungicidal product." *Id.*

These amendments to the Abstract fail to demonstrate the sort of clear reliance that would warrant construing the preamble as limiting. Pinnaclife has adduced no evidence suggesting that the amendments were made to help distinguish the '808 Patent from prior art. *See Textron Innovations Inc. v. American Eurocopter Corp.*, No. 2011-1309, 2012 WL 3871717, at *29 (Fed. Cir. Sept. 7, 2012) (holding that amendment to claim to add the term "replacement" did not limit claim where "the amended application was silent as to why the term 'replacement' was added…

[and] [t]here was no express statement… that the term 'replacement' was added to overcome the rejection by limiting the invention to replacement parts only.").[5] Accordingly, the Court finds that the amendments to the Abstract do not support the conclusion that the invention was intended to be limited to dietary supplement uses.

Pinnaclife makes one final argument regarding the prosecution history. *See* Pinnaclife's Resp. at 10-11. Pinnaclife notes that the original application for the '808 Patent included three different categories of claims. *See id.* The first two categories claimed: (1) a process of acidifying vegetation water to produce a hydroxytyrosol-rich composition (*see* Storey Decl., Ex. 7, Claims 1-9), and (2) a process of extracting a hydroxytyrosol-rich composition (*see id.*, Claims 10-16) (collectively with Claims 1-9, the "Method Claims"). The third category claimed a "dietary supplement" with a certain composition. *See id.*, Claims 17-22 ("Composition Claims"). The Method Claims were deleted from the '808 Patent during the course of prosecution leaving only the Composition Claims, which are Claims 1-6 in the final '808 Patent.[6] Pinnaclife argues that the inventor's decision to use the term "dietary supplement" rather than the term "hydroxytyrosol-rich composition" in the Composition Claims was deliberate and "for reasons relating to the prior art" such that it may be inferred that the use of the term "dietary supplement" in the preambles was intended to be limiting. *See* Pinnaclife's Resp. at 11. The Court is not persuaded. Pinnaclife provides no evidence or basis for its assertion that the term "dietary supplement" was used for reasons relating to the prior art. Consequently, this argument fails. Thus, the Court concludes that the patentee has not "clear[ly] reli[ed] on the preamble during prosecution to distinguish the claimed invention from the prior art." *Id.*, 289 F.3d at 808.

For the reasons set forth above, the Court finds that the preambles "a dietary supplement" do not establish a limitation on the claim.

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[5] Moreover, the Court notes that when the Abstract was amended to eliminate the language relating to non-dietary uses, it was also amended to eliminate language describing certain dietary uses. *See* Storey Decl., Ex. 7 at 18 (striking "it is useful as a therapeutic and anti-oxidant for a variety of health purposes").

[6] As set forth *supra*, the Method Claims were removed from the '808 Patent during prosecution pursuant to a restriction requirement. Pinnaclife's Resp., Ex. D. Many of the Method Claims (or claims similar to the Method Claims) were incorporated into a separate patent, *see* U.S. Patent No. 7,261,909, and into a continuation of the '808 Patent, *see* U.S. Patent No. 7,713,569.

C. Weight Ratios Claimed in the '808 Patent

Term in Dispute	CreAgri's Proposed Construction	Pinnaclife's Proposed Construction
Weight ratios claimed in the '808 Patent	In Claim 1 of the '808 Patent, the claimed weight ratio of hydroxytyrosol to oleuropein applies to the "aqueous extract of olives," not to the "dietary supplement." In Claim 5 of the '808 Patent, the claimed weight ratio of hydroxytytorol to tyrosol applies to the "aqueous extract of olives," not to the "dietary supplement."	In Claim 1 of the '808 Patent, the claimed weight ratio of hydroxytyrosol to oleuropein applies to the "dietary supplement." In Claim 5 of the '808 Patent, the claimed weight ratio of hydroxytytorol to tyrosol applies to the "dietary supplement."

Claims 1 and 5 of the '808 Patent describe certain weight ratios of hydroxytyrosol to oleuropein and hydroxytyrosol to tyrosol, as follows:

1. A dietary supplement comprising an aqueous extract of olives containing **a weight ratio of hydroxytyrosol to oleoeuropein[7] of between about 5:1 and about 200:1**.

5. A dietary supplement comprising an aqueous extract of olives containing **a weight ratio of hydroxytyrosol and tyrosol of between about 3:1 and about 50:1**.

'808 Patent at 10:36-38, 10:48-50 (emphasis added).

CreAgri argues that the weight ratios of the chemical compounds described in Claims 1 and 5 apply to the aqueous extract, but not to the dietary supplement. CreAgri's Opening Br. at 7-8. In other words, while the aqueous extract must contain the chemical compounds according to the claimed weight ratios, the dietary supplement need not. Pinnaclife, on the other hand, argues that

[7] The Court notes that the claims in the '808 Patent refer to "oleoeuropein" whereas the claims in the '599 Patent refer to "oleuropein." *See* '808 Patent at 10:35-39; '599 Patent at 19:45. However, the definition for "oleoeuropein" in the '808 Patent indicates that it is the same chemical as the "oleuropein" referred to in the '599 Patent. *See* '808 Patent at 4:22-23 (defining "oleoeuropein" as "secoiridoid glucoside oleuropein (Structure II in FIG. **1**)") (emphasis in original); '599 Patent at 5:15-16 (defining "oleuropein" as "secoiridoid glucoside oleuropein (Structure II in FIG. **1**)") (emphasis in original); '808 Patent, Fig. 1, Structure II; '599 Patent, Fig. 1, Structure II. Moreover, the parties use "oleuropein" in their discussion of the '808 Patent. *See e.g.* CreAgri's Opening Claim Construction Brief at 2 ("The '808 Patent… is generally directed towards water-soluble dietary supplements that contain certain claimed ratios [sic] hydroxytyrosol to *oleuropein* or tyrosol.") (emphasis added); *id.* at 5, 7. Consequently, the Court uses the terms "oleoeuropein" and "oleuropein" interchangeably.

the weight ratios in Claims 1 and 5 should apply to the dietary supplement.[8] Pinnaclife's Resp. at 11-12.

As will be set forth below, the Court finds that CreAgri's construction is supported by the claim language, but that the specification and the prosecution history fail to affirmatively support either parties' construction. Below, the Court addresses the claim language, specification, and prosecution history in turn.

1. Claim Language

As an initial matter, the Court finds that the claim language supports CreAgri's proposed construction. In Claims 1 and 5, the restrictive phrases "containing a weight ratio," follow immediately after "aqueous extract of olives" (*see* '808 Patent at 10:36-38, 10:48-50), which suggests that the weight ratios apply to the "aqueous extract." If the weight ratios were intended to apply to the "dietary supplement," additional language could have been included to make this clear. For example, the claim language could have read "[a] dietary supplement comprising an aqueous extract of olives [*and*] containing a weight ratio." *See id.* Thus, the plain language of Claims 1 and 5 supports CreAgri's proposed construction wherein the weight ratios apply to the aqueous extract.

In Pinnaclife's brief, Pinnaclife argues that the language of dependent Claims 2 and 6, which depend on Claims 1 and 5 respectively, support the conclusion that the weight ratios described in Claims 1 and 5 apply to the dietary supplement. *See* Pinnaclife's Resp. at 11-12. Claims 2 and 6 read:

> 2. The supplement of claim 1, which has a weight ratio of hydroxytyrosol to oleoeuropein of between about 10:1 and about 100:1.
>
> 6. The dietary supplement of claim 5, containing a weight ratio of hydroxytyrosol and tyrosol of between about 5:1 and about 30:1.

'808 Patent at 10:39-41; 10:51-54. Pinnaclife argues that since Dependent Claims 2 and 6 serve to further limit the weight ratios of the chemical compounds contained in the dietary supplement, the

[8] Pinnaclife argues that, because the preambles are meant to serve as a limitation on Claims 1 and 5, "it is… clear that the dietary supplement must comprise the claimed weight ratios of" chemical compounds. Pinnaclife's Resp. at 12. As set forth above, the Court has concluded that the preambles in Claims 1 and 5 were not meant to serve as a limitation on Claims 1 and 5. Furthermore, even if the preambles were meant to be limiting, it would not necessarily follow that the dietary supplement must be comprised of the claimed weight ratios.

weight ratios in Claims 1 and 5 must necessarily apply to the dietary supplement. *See* Pinnaclife's Resp. at 12. The Court disagrees.

As set forth above, Claim 1 claims:

> A dietary supplement comprising an aqueous extract of olives containing a weight ratio of hydroxytyrosol to oleoeuropein of between about 5:1 and about 200:1.

'808 Patent at 10:36-38.

Claim 2 claims:

> The supplement of claim 1, which has a weight ratio of hydroxytyrosol to oleoeuropein of between about 10:1 and about 100:1.

Id. at 10:39-41

The Court observes that because the dietary supplement described in Claim 1 is "compris[ed]" of the aqueous extract ('808 Patent at 10:36), the dietary supplement may have the same ratio of hydroxytyrosol and oleuropein as the aqueous extract. Thus, under CreAgri's proposed construction, wherein the ratio applies to the aqueous extract, Claim 1 would encompass dietary supplements "containing a weight ratio of hydroxytyrosol to oleuropein of between about 5:1 and about 200:1." *Id.* at 10:36-39. The dietary supplement claimed in Claim 2 has a narrower ratio (between 10:1 and 100:1) than the ratio described in Claim 1 (between 5:1 and 200:1). Thus, under CreAgri's construction wherein the ratio applies to the aqueous extract as opposed to the supplement, the dietary supplement in Claim 2 is still within the scope of Claim 1.

The same is true with respect to Claims 5 and 6. Claim 5 claims:

> A dietary supplement comprising an aqueous extract of olives containing a weight ratio of hydroxytyrosol and tyrosol of between about 3:1 and about 50:1.

Id. at 10:48-50.

Claim 6 claims:

> A dietary supplement comprising an aqueous extract of olives containing a weight ratio of hydroxytyrosol and tyrosol of between about 5:1 and about 30:1.

Id. at 10:51-54.

Because the dietary supplement described in Claim 5 is "compris[ed]" of the aqueous extract ('808 Patent at 10:36), the dietary supplement may have the same ratio of hydroxytyrosol and oleuropein as the aqueous extract. Thus, if the Court adopts CreAgri's construction wherein

the weight ratio described in Claim 5 applies to the aqueous extract, Claim 5 would encompass within its scope dietary supplements with a weight ratio of hydroxytyrosol and tyrosol of between about 3:1 and about 50:1. The ratio of the supplement described in Claim 6 is narrower ("between about 5:1 and 30:1") (*see id.* at 10:52-54) than the ratio described in Claim 5. Thus, under CreAgri's proposed construction, the supplement in Claim 6 would still be encompassed within the scope of Claim 5. Thus, Pinnaclife's argument fails.

Ultimately, given that the language of Claims 1 and 5 suggest that the weight ratios apply to the aqueous extract and that Pinnaclife has failed to show that Claims 2 and 6 would be excluded by CreAgri's proposed construction, the Court finds that the claim language supports CreAgri's construction. Next, the Court examines the patent specification.

2. Specification

The patent specification does not affirmatively support either parties' construction. On the one hand, the Abstract states: "The invention provides an olive-derived *dietary supplement* comprising hydroxytydrosol and oleuropein *in specific weight ratios.*" '808 Patent Abstract (emphasis added); s*ee Hill-Rom Co., Inc. v. Kinetic Concepts, Inc.*, 209 F.3d 1337, 1341 (Fed. Cir. 2000) ("[Courts] have frequently looked to the abstract to determine the scope of the invention…") (citation omitted). Thus, the Abstract seems to support Pinnaclife's construction.[9] On the other hand, in another part of the specification, the '808 Patent explicitly discloses an aqueous extract containing hydroxytyrosol and oleuropein, or hydroxytyrosol and tyrosol, at the weight ratios described in Claims 1 and 5. *See* '808 Patent at 7:50-56 ("[t]he aqueous…extracts can be formulated to contain various weight ratios of hydroxytyrosol to oleuropein of between 5:1 and 200:1… [or] hydrodxytyrosol and tyrosol of between about 3:1 and about 50:1"). There is no similar disclosure about the dietary supplement. In light of this conflicting language, the specification fails to provide convincing support for either parties' proposed construction.

[9] However, the Court notes that the Abstract is silent about the weight ratio of hydroxytyrosol and tyrosol, the two ingredients in the composition claimed in Claim 5. Accordingly, the Abstract may not even be relevant to the question of whether the weight ratio in Claim 5 applies to the supplement or the aqueous extract.

3. Prosecution History

The prosecution history of the '808 Patent also fails to conclusively support either party's construction. The Notice of Allowability states that the '808 Patent was allowed because "[n]one of the prior art references teaches or suggests the weight ratios of hydroxytyrosol to oleuropein or hydroxytyrosol to tyrosol as are instantly claimed." *See* Pinnaclife's Ex. E, ECF No. 49-6 at 3. Thus, the unique weight ratios claimed in the '808 Patent were essential in distinguishing it from the prior art. However, whether the examiner was talking about weight ratios of the chemical compounds as contained in the dietary supplement or, alternatively, in the aqueous extract is ambiguous. Other portions of the prosecution history likewise fail to clarify this point. Thus, the prosecution history fails to provide guidance as to whether the weight ratios apply to the supplement or the extract.

Because the language of Claims 1 and 5 supports CreAgri's construction, and the specification and prosecution history are ambiguous, the Court adopts CreAgri's construction that the claimed weight ratios in Claims 1 and 5 of the '808 Patent apply to the "aqueous extract of olives," not to the "dietary supplement." *See DSW, Inc. v. Shoe Pavilion, Inc.*, 537 F.3d 1342, 1347 (Fed. Cir. 2008) ("[A]bsent contravening evidence from the specification or prosecution history, plain and unambiguous claim language controls the construction analysis.").

D. Weight Ratio Claimed in the '599 Patent

Term in Dispute	CreAgri's Proposed Construction	Pinnaclife's Proposed Construction
Weight ratios claimed in the '599 Patent	In Claim 1 of the '599 Patent, the claimed weight ratio of hydroxytyrosol to oleuropein applies to the "olive plant extract," not to the "first treatment agent."	In Claim 1 of the '599 patent, the claimed weight ratio of hydroxytyrosol to oleuropein applies to the "first treatment agent."

Claim 1 of the '599 Patent also describes a certain weight ratio of hydroxytyrosol to oleuropein. The relevant part of the claim language reads:

> …administering to the subject a dose corresponding to between about 0.1 mg/kg body weight and 2000 mg/kg body weight daily of a first treatment agent comprised of an olive plant extract having **a weight ratio of hydroxytyrosol to oleuropein of between about 1:1 and about 200:1**; and…

'599 Patent at 19:41-46 (emphasis added).

Pinnaclife argues that the weight ratio applies to the "first treatment agent." *See* Pinnaclife's Resp. at 13. Pinnaclife argues that the claim language is ambiguous as to whether the weight ratio applies to the "treatment agent" or to the "olive plant extract." *Id.* Pinnaclife contends that it is, nevertheless, clear that the weight ratio applies to the treatment agent because the specification "repeatedly [describes] the treatment agent, and not the olive plant extract, as having the claimed weight ratio…." *Id.*

CreAgri argues that the weight ratio of hydroxytyrosol to oleuropein described in Claim 1 of the '599 Patent applies to the "olive plant extract." *See* CreAgri's Opening Br. at 8. CreAgri argues that the claim language only requires that the olive plant extract have the claimed weight ratio. *See id.* CreAgri also contends that Pinnaclife's argument that the weight ratio should be construed as applying to the treatment agent because the weight ratio is described as applying to the treatment agent in the specification is, in essence, an attempt to "limit[] the claimed invention… [based on the] preferred embodiments… in the specification." CreAgri's Reply at 8. (quoting *Verizon Services Corp. v. Vonange Holdings Corp.*, 503 F.3d 1295, 1302-03 (Fed. Cri. 2007)). For the reasons set forth below, the Court concludes that CreAgri's construction is correct.

As an initial matter, the Court agrees with CreAgri that the claim language supports CreAgri's proposed construction. Similar to Claims 1 and 5 of the '808 Patent, the weight ratio in Claim 1 of the '599 Patent immediately follows "olive plant extract." *See* '599 Patent at 19:43-45 ("first treatment agent comprised of an olive plant extract having a weight ratio of…."). There is no intervening language to suggest that the weight ratio was meant to apply to the first treatment agent. For example, Claim 1 does not state "a first treatment agent comprised of an olive plant extract [*and*] having a weight ratio of…." *Id.* Thus, the claim language is most consistent with CreAgri's proposed construction. Next, the Court considers the specification.

Pinnaclife argues that its construction should be adopted in part because the specification describes the weight ratio as applying to the treatment agent. *See* Pinnaclife's Resp. at 13. The Court is not persuaded. The claimed weight ratio appears a total of four times in the specification. On three of those occasions, the specification describes the weight ratio of hydroxytyrosol to

oleuropein as applying to "[the] treatment agent," as opposed to "an olive extract."[10] Of these three instances, one is particularly supportive of Pinnaclife's construction. The language is as follows:

> Summary of the Invention… In one embodiment, the weight ratio of hydroxytyrosol to oleuropein of between about 1:1 and about 200:1. In another embodiment, the weight ratio is between about 5:1 and about 100:1. In yet another embodiment, the weigth ratio of hydroxytyrosol and oleuropein is between about 10:1 and about 50:1.

'599 Patent at 2:38-44. This example is noteworthy because the referenced weight ratios (1:1 and about 200:1, 5:1 and about 100:1, and 10:1 and about 50:1), correspond exactly to the weight ratios described in the claims. *See id.* at 19:43-46 (claiming as Claim 1 a "method comprising: administering… a first treatment agent comprised of an olive plant extract having a weight ratio of hydroxytyrosol to oleuropein of between about 1:1 and about 200:1"); *id.* at 20:6-7 (claiming as dependent Claim 2, "[t]he method of claim 1, wherein said weight ratio is between about 5:1 and about 100:1); *id.* at 20:8-9 (claiming as dependent Claim 3, "[t]he method of claim 2, wherein said weight ratio is between about 10:1 and about 50:1"). The fact that the three embodiments in the specification that correspond so closely to Claims 1, 2, and 3 describe the weight ratios as applying to the treatment agent as opposed to the olive plant extract suggests that the weight ratio set forth in Claim 1 applies to the treatment agent.

Nevertheless, the Federal Circuit has cautioned that "though understanding the claim language may be aided by the explanations contained in the written description, it is important not to import into a claim limitations that are not a part of the claim." *SuperGuide Corp. v. DirecTV Enterprises, Inc.*, 358 F.3d 870, 875 (Fed. Cir. 2004). Thus, even if all the embodiments described in the specification include a certain limitation, the claims should not be construed as including this limitation unless the specification "expressly or by clear implication restrict[s] the scope of the invention." *Liebel-Flarsheim Co. v. Medrad, Inc.*, 358 F.3d 898, 908 (Fed. Cir. 2004); *id.* at 906

[10] *See* '599 Patent at 7:56-58 ("In one aspect, the invention method comprises administering to a subject… an effective amount of *a treatment agent* having a weight ratio of hydroxytyrosol to oleuropein of between about 1:1 and about 200:1."), 13:21-23 ("A dose of *an olive plant extract treatment agent* having a weight ratio of hydroxytyrosol to oleuropein of between about 1:1 and about 200:1…") (emphasis added); *but see id.* at 3:15-18 ("The method includes administering to the subject a dose of an *olive plant extract treatment agent*. In one embodiment, *the extract* has a weight ratio of hydroxytyrosol to oleuropein of between about 1:1 and about 200:1").

("Even when the specification describes only a single embodiment, the claims of the patent will not be read restrictively unless the patentee has demonstrated a clear intention to limit the claim scope using 'words or expressions of manifest exclusion or restriction.'").

Here, as set forth above, the language of Claim 1 indicates that it is sufficient for the olive plant extract to have the claimed ratio of hydroxytyrosol to oleuropein. If the Court were to nevertheless construe the weight ratio as limiting the treatment agent because the embodiments in the specification limit the treatment agent, the Court would be improperly limiting the claim based on the specification. *See e.g. SuperGuide*, 358 F.3d at 875.[11] Accordingly, the Court declines to hold that the weight ratio applies to the treatment agent simply because the embodiments set forth in the specification apply weight ratios to the treatment agent.

Thus, the Court concludes that CreAgri's construction, wherein the weight ratio applies to the "olive plant extract," is correct.

E. "aqueous extract of olives"

Term in Dispute	CreAgri's Proposed Construction	Pinnaclife's Proposed Construction
"aqueous extract of olives"	"a water-soluble preparation from an olive plant"	"an aqueous solution containing water-soluble compounds obtained by washing and pressing olive fruit" As used in the '808 Patent, "an aqueous extract" is not an "aqueous-alcoholic extract." A powder is not an "aqueous extract."

The term "aqueous extract of olives" appears in Claims 1 and 5 of the '808 Patent, as follows:

> 1. A dietary supplement comprising an **aqueous extract of olives** containing a weight ratio of hydroxytyrosol to oleoeuropein of between about 5:1 and about 200:1.

[11] The Court also notes that the embodiments in the specification -- *i.e.* those where the weight ratio applies to the treatment agent -- are not inconsistent with a construction of the claim in which the weight ratio applies to the olive plant extract. The olive plant extract is the source of hydroxytyrosol and oleuropein in the treatment agent. Thus, conceivably, the treatment agent may have the same ratio of hydroxytyrosol and oleuropein as the olive plant extract. Consequently, CreAgri's construction, which construes the ratio of hydroxytyrosol and oleuropein as applying to the olive plant extract, does not exclude the embodiments described in the specification (*i.e.* those where the treatment agent contains the claimed ratio of hydroxytyrosol and oleuropein).

5. A dietary supplement comprising an **aqueous extract of olives** containing a weight ratio of hydroxytyrosol and tyrosol of between about 3:1 and about 50:1.

'808 Patent at 10:36-38, 10:48-50 (emphasis added).

While ostensibly seeking a construction of a single term "aqueous extract of olives," the parties' constructions raise three issues. First, the parties dispute whether "aqueous extract" must be a solution, or whether it may be a dry or powder extract which was derived using water. *See* Pinnaclife's Resp. at 14 (arguing that the "aqueous extract" must be a solution); CreAgri's Opening Br. at 10 (arguing that the "aqueous extract" may be a dry powder). Second, the parties dispute whether the "olive" component of the "aqueous extract" must be derived from the olive fruit, or whether it may be derived from any part of the olive plant. *See* Pinnaclife's Resp. at 16 (arguing that the olive component must be obtained from the olive fruit); CreAgri's Opening Br. at 12-13 (arguing that the olive component may be derived from any part of the olive plant). Finally, the parties dispute whether the "olive" component must be obtained by "washing and pressing." *See* Pinnaclife's Resp. at 16 (arguing that the olive component must be obtained by "washing and pressing"); CreAgri's Opening Br. at 12 (arguing that the '808 Patent does not limit the method by which the olive component is obtained). The Court addresses each of these issues in turn.

1. "Aqueous" Means a Solution

The parties' dispute whether "aqueous extract" may be of a powdered form. Pinnaclife contends that the use of the term "aqueous" implies that the extract must be in a "watery" (*i.e.* liquid) form. Pinnaclife's Resp. at 14. Pinnaclife argues that its construction is supported by the specification, which indicates that the aqueous extract is a solution. *See id.* at 15.

CreAgri argues that "aqueous extract" may refer to a powdered extract so long as it is derived from water. *See* CreAgri's Opening Br. at 11. CreAgri contends that the word "aqueous" merely describes the origin of the compound, meaning that it was collected in water, rather than describing the current state of the compound. *See id.* at 9, 11. CreAgri argues that interpreting the term aqueous extract as requiring a watery or liquid substance would exclude dependent Claim 3. *See id.* at 11. At the *Markman* hearing, CreAgri also argued that dependent Claim 4 supports its construction. *See* Tr. at 108:1-6. Finally, CreAgri argues in its briefs that the extrinsic evidence,

specifically the dictionary definition of "aqueous," supports CreAgri's proposed construction. *See* CreAgri's Opening Br. at 10.

The Court finds that Pinnaclife's proposed construction is correct based on the specification. The Court is not persuaded by CreAgri's arguments that CreAgri's interpretation is necessary so as not to exclude Claim 3 or CreAgri's argument that its interpretation must be adopted based on the extrinsic evidence. Below, the Court addresses: (1) Pinnaclife's arguments regarding the specification; (2) CreAgri's arguments regarding dependent Claims 3 and 4; and (3) CreAgri's arguments regarding the extrinsic evidence.

a. Specification

As an initial matter, the Court agrees with Pinnaclife that its construction is the most consistent with the specification. *See In re Abbott Diabetes Care Inc. ("Abbott")*, 696 F.3d 1142, 1149 (Fed. Cir. 2012) ("Although the PTO emphasizes that it was required to give all claims their broadest reasonable construction, ... this court has instructed that any such construction be consistent with the specification."); *see also Burlington Indus., Inc. v. Dayco Corp.*, 849 F.2d 1418, 1421 (Fed. Cir. 1988) ("[I]t is said the inventor may be his own lexicographer…But he must use his words consistently in the claims and in the specifications."). The term "aqueous extract" appears three times in the specification.[12] In two of those instances, the specification merely recites the claim language. *See* '808 Patent at 3:43-51. The third instance, however, is enlightening. It reads:

> Oral dosage forms [of hydroxytyrosol] can be in solid or liquid form. Such dosage forms can be formulated from purified hydroxytyrosol or they can be formulated from *aqueous or aqueous-alcoholic extracts.* Regarding the latter, *aqueous or aqueous-alcoholic…extracts can be spray-dried to provide a dry powder* that can be formulated into oral dosage forms with other pharmaceutically acceptable carriers.

'808 Patent at 7:41-50 (emphasis added). The fact that the aqueous extract must be *dried* to

[12] Although not directly using the term "aqueous extract," the Background of the Invention also states that "it is desirable to develop a method which produces an *aqueous olive extract* with a high percentage of hydroxytyrosol." '808 Patent at 2:52-54 (emphasis added). This statement, however, does not provide sufficient information to be of assistance in resolving the parties' dispute.

provide a dry powder suggests the aqueous extract itself is not already in a dry form. *See id.*[13]

Notably, CreAgri appears to read the aforementioned statement regarding the spray-drying of the aqueous extract into a dry power as an indication that the aqueous extract may be dry. *See* CreAgri's Opening Br. at 10 (citing '808 Patent at 7:42-50). Indeed, the Court might agree with CreAgri if the specification continued to refer to the extract as "aqueous extract" after the point of spray-drying. However, the sentences following the spray-drying sentence address additional characteristics of the aqueous extract and do not indicate whether the extract would continue to be referred to as an "aqueous" extract after spray-drying.[14]

The Court also notes that, to the extent the specification uses adjectives to describe dry forms of the extract, the specification uses the adjectives "dried" or "powder." For example, the specification states that "the vegetation water of isolated hydroxytyrosol [may be used] to produce a *dried* extract." '808 Patent at 3:10-11 (emphasis added). In another instance, the specification states that: "The above supplements may be dried to provide a *powder* extract, which can [be] formulated into a tablet, capsule, pill, or confection food additive." *Id.* at 3:52-54 (emphasis added). These uses suggest that, where the inventor intended to refer to a dry extract, the inventor referred to it using a term other than aqueous extract.

Thus, the Court finds that the specification supports Pinnaclife's proposed construction wherein the use of the term "aqueous" implies that the extract must be in a watery or liquid form.[15]

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[13] Indeed, definitions of spray-drying expressly state that the substance being spray-dried must be a fluid. *See* Perry's Chemical Engineers' Handbook, 7th Edition (1997) (defining spray-drying as "[f]eed solids in a *fluid state* (solution, gel, paste, emulsion, slurry, or melt) are dispersed in a gas and converted to granular solid products by heat.") (emphasis added); Hawley's Condensed Chemical Dictionary, 13th Edition (1997) (defining "spray-dry" as "drying solids by spraying *solutions of them* into a heated chamber.") (emphasis added).

[14] For example, the sentence in the specification following the spray-drying sentence provides that the "aqueous extract" may be "formulated to contain various weight ratios of hydroxytyrosol to oleoeuropein." '808 Patent at 7:50-53. It gives no indication as to whether an extract that has been spray-dried would continue to be an "aqueous" extract.

[15] At the *Markman* hearing, when asked what part of the specification supported its construction that "aqueous extract" may be dry, CreAgri pointed to 8:28-34 of the '808 Patent. *See* Tr. 106:8-10. It reads "[Parenteral formulations] are commonly prepared as sterile injectable solutions, using a parenterally acceptable carrier such as isotonic saline solution or as a sterile packaged powder prepared for reconstitution with sterile buffer or isotonic saline prior to administration to a subject." While this paragraph appears to disclose a "powder," nowhere does it make clear that the "aqueous extract" is the powder.

b. Dependent Claims 3 and 4

CreAgri argues that construing "aqueous extract" as a solution would exclude Dependent Claim 3. *See* CreAgri's Opening Br. at 11. Claim 3 reads:

> The supplement of claim 1, wherein said supplement *is dried* to provide a powder extract.

'808 Patent at 10:42-43 (emphasis added). Citing to the principle that a dependent claim must "include every limitation of the claim from which it depends…", CreAgri contends that, if Claim 1 is construed as including a limitation pursuant to which the extract must be a liquid, Claim 3 will be excluded because it does not include this limitation, but instead permits a dry, "powder extract." *See* CreAgri's Opening Br. at 11 (quoting MPEP § 608.01). The Court is not persuaded.

Claim 3 does not indicate that the "aqueous extract" may be a dry powder. For example, Claim 3 does not state that "the supplement of claim 1, wherein said aqueous extract is a powder extract." Instead, Claim 3 specifies that the dietary supplement in Claim 1 may be *dried*. This is entirely consistent with the interpretation that "aqueous extract" is a solution. Claim 3 simply implies that the supplement, which is comprised of an aqueous extract, may become a "powder extract" after undergoing a drying process.[16] Claim 3 does not imply that the aqueous extract is dry in its original form. Claim 3 therefore does not omit the limitation that the aqueous extract is a liquid.[17] Thus, construing Claim 1 as requiring a liquid extract would not exclude Claim 3.

At the *Markman* hearing, CreAgri argued, for the first time, that dependent Claim 4 also supports CreAgri's proposed construction. *See* Tr. 108:1-6. Claim 4 recites, "The dietary supplement of claim 1, wherein said extract is in the form of a tablet, capsule, pill, or confection food additive." '808 Patent at 10:45-47. The only extract to which Claim 1 refers is the "aqueous extract." It could be argued that because Claim 4 indicates that the extract may be in the form of a tablet, which is dry, then the aqueous extract may be dry, as opposed to a solution. The Court is

[16] Notably, the language of Claim 3 states the "*supplement*" becomes a "powder *extract*" after being "dried." '808 Patent at 10:43-44 (emphasis added). There is no explanation as to why a *supplement*, which is comprised of an extract and potentially other ingredients, is referred to as an *extract* after it is dried. *See supra* Section III(B).

[17] The Court further observes that in Claim 3 the inventor again uses a term other than "aqueous extract" to describe a dried version of the extract (i.e., "a powder extract").

not persuaded that Claim 4 provides a sufficient basis to construe aqueous extract as including dry powders.

Notably, the specification indicates that the extract must be processed before it can be formed into a tablet, capsule, pill, or confection food additive. Specifically, the specification states that, in order to be formed into a tablet, capsule, pill, and confection food additive form, a "hydroxytyrosol-rich composition," which may be in the form of an "extract," must be "mixed, diluted, or enclosed with a carrier." *See id.* at 7:61-64. In some instances, the composition may also be combined with additional elements including sugars, other flavoring agents, starches, emulsifiers, and preservatives. *See id.* at 8:11-22. These statements imply that, in order to be formed into a tablet, capsule, pill, and confection food additive form, the aqueous extract must be mixed, diluted, or otherwise altered. Thus, in light of the specification, Claim 4's statement that the aqueous extract "is in the form of a tablet, capsule, pill, or confection food additive," does not necessarily support the conclusion that the aqueous extract was originally dry, but rather supports the conclusion that the aqueous extract may be processed into a dry form. Because it appears from the specification that the extract to which Claim 4 refers must be processed into a dry form, the Court finds that Claim 4 does not support the conclusion that the aqueous extract may be dry.[18]

c. Extrinsic Evidence

The Court is also not persuaded by CreAgri's extrinsic evidence. CreAgri argues that the definition of "aqueous," as set forth in the McGraw-Hill Dictionary of Scientific Terms, supports

[18] The Court is also reluctant to rely on Claim 4 because it is not clear that Claim 4's statement that the *extract* may be in the form of a tablet, capsule, pill, or confection food additive is accurate. The specification suggests that it is the *supplement* rather than the aqueous extract that may be in the form of a tablet, capsule, pill, or confection food additive. Specifically, the specification provides that: "The above *supplements* may be dried to provide a powder extract, which can [be] formulated into a tablet, capsule, pill, or confection food additive." *Id.* at 3:52-54 (emphasis). However, Claim 4 states that the "*extract* [may be] in the form of a tablet, capsule, pill, or confection food additive." '808 Patent at 10:45-47. Given that the supplement is the final form of the product, it is logical that it would be in an easily consumable form such as a tablet, capsule, pill, or confection food additive. It is not necessarily clear that there would be a reason for the extract, which is a mere component of the final product, to be processed into a tablet, capsule, pill, or confection food additive. Consequently, the Court has concerns that, in stating that the *extract* may be in the form of a tablet, capsule, pill, or confection food additive in Claim 4, the inventor may have incorrectly substituted the term "extract" for "supplement."

its construction. *See* CreAgri's Opening Br. at 10. The McGraw-Hill Dictionary of Scientific Terms defines "aqueous" as "[r]elating to or made with water." *See* Storey Decl., Ex. 4 (McGraw-Hill Dictionary of Scientific Terms, 4th Ex., 1989) at 114.[19] CreAgri argues that it may be inferred from the aforementioned definition that "aqueous" only means that the extract must be extracted using water, not that it must still be in a liquid state. *See* CreAgri's Opening Br. at 10.

CreAgri's reliance on the dictionary definition is misplaced. As an initial matter, CreAgri's dictionary definition is from 1989, which is more than a decade before the 2001 effective filing date of the patent application. *See Phillips*, 415 F.3d at 1313 ("the ordinary and customary meaning of a claim term is the meaning that the term would have to a person of ordinary skill in the art in question *at the time of the invention, i.e., as of the effective filing date of the patent application*.") (emphasis added). Moreover, CreAgri's definition provides only limited support for CreAgri's position that the aqueous extract may be dry as the use of the phrase "relating to… water" is not necessarily broad enough to permit a watery solution that has been dried. Furthermore, even if the dictionary definition did support CreAgri's position, extrinsic evidence like the dictionary definition is "less significant than the intrinsic record." *See Phillips*, 415 F.3d at 1317 ("[W]hile extrinsic evidence can shed useful light on the relevant art,…it is less significant than the intrinsic record in determining the legally operative meaning of claim language" (internal quotations omitted)). Here, as discussed above, the only reference to the aqueous extract in the specification that gives any indication of its states indicates that it is a liquid, and, in several cases where the specification refers to a dried extract, it refers to it using the adjectives "dried" and "powdered." Thus, the intrinsic evidence in this case supports the conclusion that the use of the adjective "aqueous" in connection with the term "extract" implies that the extract is still in a liquid form.

Ultimately, given that the only reference to aqueous extract in the specification that gives any indication of the extract's state indicates that it is a liquid, the Court agrees with Pinnaclife that

[19] CreAgri further notes that "extract" is defined as "a preparation, usually in concentrated form, obtained by treating plant… tissue with a solvent to remove desired … nutritive components." *Id.* at 684.

the term "aqueous extract" refers to a liquid extract, as opposed to merely referring to an extract that was originally obtained using water as a solvent. Thus, the Court construes the term "aqueous extract" as "an aqueous solution containing a water-soluble preparation." Next, the Court addresses the parties' dispute regarding whether the olive component of the aqueous extract must be obtained from the olive fruit or whether it may be obtained from any part of the olive plant.

2. "Olives" Do Not Refer Only to Olive Fruits

Pinnaclife contends that, as used in the '808 Patent, "olives" refer only to the olive fruits and that, accordingly, the "aqueous extract of olives" must be derived only from olive fruit. Pinnaclife's Resp. at 16-17. In support of this argument, Pinnaclife notes that the '808 Patent specification describes various methods for producing hydroxytyrosol-rich compositions. *See id.* at 16.[20] In describing these methods, the specification repeatedly references "olives" together with words that are characteristic of olive fruits such as "pits," "pulps" and "olive meat." *Id.* Pinnaclife argues that these references support the conclusion that "olives" refer to olive fruit. *Id.*

CreAgri argues that "olives" refer to the entire olive plant and not just the fruits. CreAgri's Opening Br. at 12. CreAgri argues that the claim language does not refer to olive *fruits*, and that the prosecution history also does not provide any indication that "the compositions had to be limited to extracts only from the olive fruit." *Id.* CreAgri argues that, by attempting to construe olives as referring to only the olive fruit based on the references to olive meat and other portions of the olive fruit in the specification, Pinnaclife is "inappropriately read[ing] a limitation from the written description into the claims." *Id.* (citing *Phillips*, 415 F.3d at 1323). The Court agrees with CreAgri that the term "olives" should not be construed as referring exclusively to the olive fruit.

Pinnaclife is correct that, in describing the methods for producing hydroxytyrosol-rich compositions, the patent specification repeatedly references "olives" together with words that are characteristic of olive fruits (*e.g.* "pits," "pulps" and "olive meat"). *See, e.g.*, '808 Patent at 2:31-32 ("[O]live oil production involves crushing *olives*, including the *pits*, to produce a thick paste."),

[20] As set forth *supra*, the application for the '808 Patent included a number of Method Claims, but these claims were deleted from the final version of the '808 Patent. However, the descriptions of these methods in the specification remain.

4:43-44 ("*Pits* in the *olives* contain tyrosol which is an undesired component in the vegetation water…"), 4:53-55 ("To produce vegetation water, *olive pulp* from the *olives* is first pressed to obtain a liquid-phase mixture including olive oil…"), 5:1-3 ("Initially, *olives* are fed to a pulper that separates the *olive pits* from the *olives* to obtain a *pitless olive meat*." (emphasis added)). However, this does not necessarily mean that the invention requires that the olive component be derived from olive fruit.

As set forth *supra*, the Federal Circuit has cautioned that, "[t]hough understanding… claim language may be aided by the explanations contained in the written description," a court cannot "import into a claim limitations" from the written description. *SuperGuide*, 358 F.3d at 875. Thus, even if all the embodiments described in the common specification include a certain limitation, the claims should not be construed as including this limitation unless the specification "expressly or by clear implication restrict[s] the scope of the invention." *Liebel-Flarsheim*, 358 F.3d at 908; *id.* at 906.

In this case, although the patentee repeatedly references the term "olives" together with words characteristic of olive fruits (*e.g.* "pits," "pulps" and "olive meat"), nowhere in the specification does the patentee "expressly or by clear implication restrict" the term "olive" to olive fruits or reject the use of other components of the olive plant to obtain the claimed extract. *See Liebel-Flarsheim Co.*, 358 F.3d at 908. Indeed, the Field of the Invention indicates that any part of the olive plant may be used to the extent it states that "[t]his invention relates to a phenolic fraction of a group of compounds present in *olive plants* known as hydroxytyrosol…" '808 Patent at 1:10-11. Accordingly, the Court declines to construe the term "olives" in Claims 1 and 5 of the '808 Patent as being limited to "olive fruits."

3. The Dietary Supplement Need Not Be Obtained Through "Washing and Pressing Olive Fruit"

Pinnaclife next argues that the dietary supplement of the invention must be obtained through the process of "washing and pressing olive fruit." Pinnaclife's Resp. at 17. CreAgri urges that no such limitation should be read into the claims. CreAgri's Opening Br. at 12-13. The Court agrees with CreAgri.

The Federal Circuit has held that a true product claim, as opposed to a product-by-process claim, is not limited to the methods of manufacture disclosed in the specification. *Vanguard Products Corp. v. Parker Hannifan Corp.*, 234 F.3d 1370, 1372-73 (Fed. Cir. 2000) ("A novel product that meets the criteria of patentability is not limited to the process by which it was made."); *Andersen Corp. v. Fiber Composites*, 474 F.3d 1361 (Fed. Cir. 2007) ("[T]he method of manufacture, even when cited as advantageous, does not itself convert product claims into claims limited to a particular process…"); *Compare Southwall Technologies, Inc. v. Cardinal IG Co.*, 54 F.3d 1570 (Fed. Cir. 1995) (process steps can be treated as part of a product claim if the patentee has made clear that the process steps are an essential part of the claimed invention).

Here, Claims 1 and 5 of the '808 Patent are product claims defined in terms of structural characteristics alone. Moreover, the prosecution history confirms that the patent was allowed because of the unique structural characteristics of the claimed product and not because of the method in which it is produced. *See* Pinnaclife's Ex. E, ECF No. 49-6 at 3 (Notice of Allowability stating that the '808 Patent was allowed because "[n]one of the prior art references teaches or suggests the weight ratios of hydroxytyrosol to oleuropein or hydroxytyrosol to tyrosol as are instantly claimed."). Indeed, the patent examiner recognized that "the product may be prepared by more than one method," and that "one could prepare the composition of [the invention] by merely physically mixing the known components of the composition." *See* Office Action, ECF No. 47-7 at 4. Thus, the Court concludes that the dietary supplement of the invention need not be obtained through "washing and pressing olive fruit" as Pinnaclife proposes. *See Vanguard*, 234 F.3d at 1372-73.

Having addressed each of the parties' disputes concerning the proper interpretation of the term "aqueous extract of olives," the Court construes this term as "an aqueous solution containing a water-soluble preparation from an olive plant," with no restriction on the process by which the "aqueous solution" is obtained.

F. "clinical symptom" or "detectable clinical symptom"

Terms in Dispute	CreAgri's Proposed Construction	Pinnaclife's Proposed Construction
"clinical	No construction necessary.	"subjective evidence of disease or

symptom" or "detectable clinical symptom"		physical disturbance perceived by the patient and observed by a physician during clinical examination" "Clinical symptom" or "detectable clinical symptom," as used in the '599 Patent, refers only to (1) respiratory distress associated with bronchial inflammation or (2) clinical symptoms determined from neuropsychological testing where those symptoms are associated with neuro-inflammation, and excludes all other symptoms.

The term "clinical symptom" and "detectable clinical symptom" both appear in Claim 1 of the '599 Patent, as follows:

> 1. A method of treating a subject having an inflammatory condition characterized by a **detectable clinical symptom** or change in a level of a biochemical marker with respect to the normal range of the marker, the method comprising:
>
> administering to the subject a dose corresponding to between about 0.1 mg/kg body weight and 2000 mg/kg body weight daily of a first treatment agent comprised of an olive plant extract having a weight ratio of hydroxytyrosol to oleuropein of between about 1:1 and about 200:1; and
>
> continuing said administration until there is observed a return of the marker level to the normal range or a desired change in the **clinical symptom**,
>
> where the marker or the **clinical symptom** is selected from the group consisting of
>
> (i) elevated levels of C-reactive protein in the case of coronary inflammation;
>
> (ii) respiratory distress in the case of bronchial inflammation; and
>
> (iii) elevated CSF levels of isoprostanes or clinical symptoms determined from neuropsychological testing in the case of neuro inflammation.

'599 Patent at 19:37-20:5 (emphasis added).

CreAgri argues that "clinical symptom" is a plain, non-technical term that should be given its ordinary meaning. CreAgri's Opening Br. at 20. Pinnaclife argues that "clinical symptom" should be construed as requiring observation by both a patient and a physician. Pinnaclife's Resp. at 18. In addition, Pinnaclife urges this Court to limit the scope of "clinical symptom" to only two conditions explicitly stated in Claim 1. *Id.* at 19-20. The Court addresses each of these arguments below.

1. "Clinical Symptom" Does Not Require the Observation of a Physician or a Patient

Pinnaclife argues that the term "clinical symptom" should be construed as requiring that the symptom be observed by both a patient *and* a physician. *See* Pinnaclife's Resp. at 18-19. As stated by Pinncalife at the *Markman* hearing, Pinnaclife's primary purpose in pursuing this construction is to ensure that the jury understands that the symptom must be observed by a *physician* in addition to the patient. *See* Tr. at 74:16-23. Pinnaclife argues that its construction is supported by the specification, extrinsic evidence (specifically, two dictionary definitions), and the statements of CreAgri's counsel at the October 16, 2012 hearing on Pinnaclife's motion to compel. *See* Pinnaclife's Resp. at 18-19.

CreAgri argues that no construction of "clinical symptom" is necessary, and that Pinnaclife's construction is incorrect. *See* CreAgri's Opening Br. at 20-21; CreAgri's Reply at 12-13. In particular, CreAgri takes issue with Pinnaclife's proposed construction to the extent it requires observation by a physician. *See id.* CreAgri argues that Pinnaclife's proposed construction is not supported by the claim language or the specification, and that Pinnaclife's reliance on the dictionary definitions and CreAgri's counsel's statements at the October 16, 2012 hearing is misplaced. *See id*.

The Court agrees with CreAgri that the term "clinical symptom" should not be construed to require observation by both the patient and a physician. The Court addresses the parties' arguments regarding: (1) the claim language; (2) the specification; (3) the extrinsic evidence; and (4) CreAgri's counsel's statements in turn.

With respect to the claim language, the Court observes that neither "physician," "patient," nor any similar terms appear in the claim language. *See* '599 Patent at 19:37-20:5. Claim 1 merely states that "there *is observed*…a desired change in the clinical symptom," without specifying who must observe the symptom. '599 Patent at 19:47-49; *See NTP, Inc. v. Research In Motion, Ltd.*, 418 F.3d 1282, 1310 (Fed. Cir. 2005) (the court cautioned against including elements not mentioned in the claim in order to limit such claim) (citing *McCarty v. Lehigh Valley R. Co.*, 160 U.S. 110, 116 (1895)). Thus, the claim language does not support Pinnaclife's construction that the clinical symptom must be observed by the patient and a physician.

Pinnaclife's construction also finds no support in the specification. The term "symptom" or "clinical symptom" appears eight times in the specification. The specification indicates that a "clinical symptom" is one that is "detectable" and observable. *See, e.g.*, '599 Patent at 3:13 ("a detectable clinical symptom"), 3:23-24 ("…until there is observed a return of the marker level to the normal range or a desired change in the clinical symptom."). However, like the claim language, the specification does not indicate whether a patient, a physician, or both must observe the clinical symptom. Indeed, the specification only makes a passing reference to "physician," and this reference does not suggest that a physician must observe the clinical symptom. *See* '599 Patent at 4-6 ("It will be understood that the amount of the compound actually administered will be determined by a physician…"). Similarly, while the word "patient" appears more often throughout the specification, it is generally associated with a certain type of disease. *See, e.g.*, '599 Patent at 9:15-16 ("…treating a patient suffering from peripheral neuropathy."). The specification does not give any indication that the "clinical symptom" must be observed by the patient and a physician.

Pinnaclife's citations to extrinsic evidence are also unavailing. Pinnaclife contends that its assertion that the symptom must be observed by both the patient and a physician is supported by two dictionary definitions of "clinical." Pinnaclife's Resp. at 18. The first definition, which is from the 2002 edition of Webster's Third International Dictionary, defines "clinical" as "involving or depending on direct observation of the living patient; observable by clinical inspection." *See* Marshall Decl. ¶ 12, Ex. K (Webster's Third Int'l Dictionary). The second definition, which is from the 2006 edition of the American Heritage Dictionary, defines "clinical" as "involving or relating to direct observation of the patient." *See* Marshall Decl. ¶ 11, Ex. J (Am. Heritage Dictionary).

At the outset, the Court notes that the definition from the 2006 edition of the American Heritage Dictionary does not provide particularly probative evidence regarding the proper construction of the terms of the '599 Patent because this patent was filed three years earlier on Feb. 13, 2003.[21] *See Phillips*, 415 F.3d at 1313 ("the ordinary and customary meaning of a claim term is

[21] The Provisional Application of the '599 Patent was filed on Feb. 13, 2002.

the meaning that the term would have to a person of ordinary skill in the art in question *at the time of the invention, i.e., as of the effective filing date of the patent application*.") (emphasis added). Moreover, while Pinnaclife's dictionary definitions define "clinical symptoms" as requiring "direct observation," neither definition requires observation by a "physician" as Pinnaclife contends. Furthermore, as a practical matter, in many instances, medical personnel other than a physician may be charged with observing patients. Thus, contrary to Pinnaclife's assertion, the dictionary definition does not support its construction.

Finally, Pinnaclife directs the Court to a statement by CreAgri's counsel that suggests a doctor is required to observe the "clinical symptom." *See* Pinnaclife's Resp. at 19. CreAgri's counsel made the statement during the hearing on Pinnaclife's motion to compel supplemental infringement contentions, which reads:

> Q: Is it your theory that the doctor will make [the determination that the inflammation is gone] or is it that the customer takes the bill [sic] and is done?
>
> A: I think when the doctor determines the inflammation is gone.

Pinnaclife's Resp. Ex. L, ECF No. 49-13 at 25:17-26:13. The Court is not persuaded. First, Pinnaclife points to no authority that instructs the Court to rely on counsel's statement made during a discovery hearing to interpret the meaning of a disputed claim term. *Cf. Phillips v. AWH Corp.*, 415 F.3d 1303, 1317 (Fed. Cir. 2005) (aside from intrinsic evidence, the court also authorizes district courts to rely on evidence "external to the patent and prosecution history, including expert and inventor testimony, dictionaries, and learned treatises.") (citation omitted). Even if counsel's statement was proper evidence for claim construction, it cannot trump intrinsic evidence such as the claim language and the specification. *See id.* (holding that "extrinsic evidence… is less significant than the intrinsic record") (internal quotations omitted). As explained above, the intrinsic evidence imposes no limitation that a physician or a patient must observe the "clinical symptom." Thus, the Court declines to read this limitation into Claim 1 of the '599 Patent.

For the reasons set forth above, the Court concludes that the term "clinical symptom" does not imply that the symptom must be observed by both the patient and a physician.

2. "Clinical Symptom" Refers Only to the Two Symptoms Explicitly Disclosed in Claim 1

Pinnaclife next argues that "clinical symptom" should be construed as referring to only those symptoms specifically identified in the claim. *See* Pinnaclife's Resp. at 19-20.

The relevant claim language reads "where the marker or clinical symptom is selected from the group *consisting of* (i) elevated levels of C-reactive protein in the case of coronary inflammation; (ii) respiratory distress in the case of bronchial inflammation; and (iii) elevated CSF levels of isoprostanes or clinical symptoms determined from neuropsychological testing in the case of neuro inflammation." '599 Patent at 19:50-20:5 (emphasis added). The parties agree that "respiratory distress in the case of bronchial inflammation" and "clinical symptoms determined from neuropsychological testing in the case of neuro inflammation" are "clinical symptom[s]." *See* Tr. 65:9-18; Pinnaclife's Resp. at 18. The parties also agree that: (1) "elevated levels of C-reactive protein in the case of coronary inflammation," and (2) "elevated CSF levels of isoprostanes" are "marker[s]." *See* Tr. 65:9-18; Pinnaclife's Resp. at 18.

Pinnaclife argues that the fact that the list of markers and symptoms is preceded by the term "consisting of" implies that the only two symptoms encompassed in the claim language are: (1) "respiratory distress in the case of bronchial inflammation," and (2) "clinical symptoms determined from neuropsychological testing in the case of neuro inflammation." *See* Pinnaclife's Resp. at 20. The Court agrees. In contrast to the term "comprising of," the term "consisting of" is "well understood in patent usage… [to be] close-ended and convey limitation and exclusion." *CIAS, Inc. v. Alliance Gaming Corp.*, 504 F.3d 1356, 1361 (Fed. Cir. 2007); *see also Norian Corp. v. Stryker Corp.*, 363 F.3d 1321, 1331 (Fed. Cir. 2004) ("'[C]onsisting of' is a term of patent convention meaning that the claimed invention contains only what is expressly set forth in the claim...."). Thus, the patent drafter's use of the phrase "consisting of," as opposed to "comprising of," suggests that "clinical symptom" should be limited to the two symptoms explicitly stated in the claim.

At the *Markman* hearing, CreAgri generally agreed that "clinical symptom" should be limited to the symptoms explicitly stated in the claim. *See* Tr. at 117:9-12. However, CreAgri urged the Court to construe "clinical symptom" to include "coronary inflammation," in addition to "respiratory distress…" and "clinical symptoms determined from neuropsychological testing…"

See id. at 118:18-119:15; '599 Patent at 19:53. The Court is not persuaded. The term "coronary inflammation" appears in the following claim language: "elevated levels of C-reactive protein *in the case of coronary inflammation*." '599 Patent at 19:52-53 (emphasis added). As set forth *supra*, CreAgri has agreed this statement as a whole refers to a marker and not a symptom. Moreover, CreAgri fails to direct the Court's attention to any intrinsic evidence supporting its assertion that "coronary inflammation" constitutes a separate clinical symptom. Thus, the Court declines to construe "clinical symptoms" as including "coronary inflammation."[22]

Thus, for the reasons stated above, "clinical symptom" or "detectable clinical symptom," as used in the '599 Patent, refers only to (1) respiratory distress in the case of bronchial inflammation, or (2) clinical symptoms determined from neuropsychological testing where those symptoms are related to neuro-inflammation. The Court further clarifies that Claim 1 of the '599 Patent does not include the limitation that a physician or a patient must observe the "clinical symptom" or "detectable clinical symptom."

G. "marker" or "biochemical marker"

Terms in Dispute	CreAgri's Proposed Construction	Pinnaclife's Proposed Construction
"marker" or "biochemical marker"	No construction necessary.	"a biological substance measured, detected, or observed by a physician to evaluate the presence of inflammation" "Marker" or "biological marker," as used in the '599 patent, refers only to (1) C-reactive protein in the case of coronary inflammation or (2) CSF levels of isoprostanes in the case of neuro-inflammation, excludes all other biological substances.

[22] The Court notes that the specification does list one additional symptom: "joint pain and swelling in the case of joint inflammation," *see* '599 Patent at 13:33-36. However, this symptom is not listed in the claim language. Moreover, at the *Markman* hearing, CreAgri conceded that the inventor had disavowed "joint pain and swelling" as a symptom. *See* Tr. at 68:20-64:6; Marshall Decl., Ex. H ("The Examiner's attention is drawn to the fact that *the claims no longer recite symptoms such as those related to joint inflammation*. Thus, the Examiner's remarks directed to this previously claimed aspect of the method are now rendered moot."). Accordingly, the Court does not construe "clinical symptom" as including "joint pain and swelling in the case of joint inflammation."

The terms "marker" and "biochemical marker" both appear in Claim 1 of the '599 Patent, as follows:

> 1. A method of treating a subject having an inflammatory condition characterized by a detectable clinical symptom or change in a level of a **biochemical marker** with respect to the normal range of the **marker**, the method comprising:
>
> administering to the subject a dose corresponding to between about 0.1 mg/kg body weight and 2000 mg/kg body weight daily of a first treatment agent comprised of an olive plant extract having a weight ratio of hydroxytyrosol to oleuropein of between about 1:1 and about 200:1; and
>
> continuing said administration until there is observed a return of the **marker** level to the normal range or a desired change in the clinical symptom,
>
> where the **marker** or the clinical symptom is selected from the group consisting of:
>
> (i) elevated levels of C-reactive protein in the case of coronary inflammation;
> (ii) respiratory distress in the case of bronchial inflammation; and
> (iii) elevated CSF levels of isoprostanes or clinical symptoms determined from neuropsychological testing in the case of neuro inflammation.

'599 Patent at 19:37-20:5 (emphasis added).

CreAgri argues that no construction is necessary. *See* CreAgri's Opening Br. at 20. Pinnaclife, on the other hand, argues that the term should be construed as meaning "a biological substance measured, detected, or observed by a physician to evaluate the presence of inflammation." Pinnaclife's Resp. at 20-21. Pinnaclife further argues that "marker" or "biochemical marker" refers only to the markers explicitly set forth in the claim. *See id.* at 20.

The Court disagrees with Pinnaclife that a physician must measure, detect or observe the marker or biochemical marker. As set forth above in connection with the related term "clinical symptom," the intrinsic evidence does not support including this additional limitation. Neither the claim language nor the specification requires that the marker be measured, detected or observed by a physician. CreAgri's counsel's statement that a physician must determine the presence or absence of inflammation, even assuming the statement is proper evidence for claim construction, cannot trump the intrinsic evidence. *See* Pinnaclife's Resp. Ex. L, ECF No. 49-13 at 25:17-26:13.

Thus, as with "clinical symptom," there is no requirement that a physician must measure, detect or observe the marker or biochemical marker.

The Court does, however, agree with Pinnaclife that "marker" or "biochemical marker" should be limited to the two markers expressly set forth in the claim language ("elevated levels of C-reactive protein in the case of coronary inflammation" and "elevated CSF levels of isoprostanes in the case of neuro-inflammation"). As noted above, the transition phrase "consisting of" is unambiguously close-ended, conveying limitation and exclusion. *See CIAS*, 504 F.3d at 1361.

Accordingly, the Court construes "marker" or "biochemical marker" as referring only to (1) elevated levels of C-reactive protein in the case of coronary inflammation or (2) elevated CSF levels of isoprostanes in the case of neuro-inflammation. *See* '599 Patent at 19:50-20:5.[23] The Court further clarifies that Claim 1 of the '599 Patent does not include the limitation that a physician must measure, detect or observe the marker or biochemical marker.

H. Conclusion

For the reasons discussed above, the Court construes the disputed claim terms as follows:

Claim Language	**Construction**
"comprising" or "comprised of"	"including but not limited to"
the preamble "a dietary supplement" in Claims 1 and 5 of the '808 Patent	the preamble "a dietary supplement" in Claims 1 and 5 of the '808 Patent is not a claim limitation.
weight ratios claimed in the '808 Patent	the claimed weight ratios in Claims 1 and 5 of the '808 Patent apply to the "aqueous extract of olives," not to the "dietary supplement."
weight ratio claimed in the '599 Patent	the claimed weight ratio in Claim 1 of the '599 Patent apply to the "olive plant extract."
"aqueous extract of olives"	"an aqueous solution containing a water-soluble preparation from an olive plant," with no restriction on the process by which the "aqueous solution" is obtained.

[23] In Pinnaclife's proposed construction for "markers," neither "levels of C-Reactive protein…" nor "CSF levels of isoprostanes…" is preceded by the word "elevated." Because the claim language includes the word "elevated" before both markers, *see e.g.* '599 Patent at 19:52 ("elevated levels of C-reactive protein"), and the parties used the word "elevated" in connection with both markers at the *Markman* hearing, *see e.g.* Tr. at 65:9-14, the Court includes "elevated" in its final construction.

"clinical symptom" or "detectable clinical symptom"	"clinical symptom" or "detectable clinical symptom," as used in the '599 Patent, refers only to (1) respiratory distress in the case of bronchial inflammation, or (2) clinical symptoms determined from neuropsychological testing where those symptoms are related to neuro-inflammation. Claim 1 of the '599 Patent does not include the limitation that a physician or a patient must observe the "clinical symptom" or "detectable clinical symptom."
"marker" or "biochemical marker"	"marker" or "biochemical marker," as used in the '599 Patent, refers only to (1) elevated levels of C-reactive protein in the case of coronary inflammation or (2) elevated CSF levels of isoprostanes in the case of neuro-inflammation. Claim 1 of the '599 Patent does not include the limitation that a physician must measure, detect or observe the marker or biochemical marker.

IT IS SO ORDERED.

Dated: April 16, 2013

LUCY H. KOH
United States District Judge

US006416808B1

(12) **United States Patent**
Crea

(10) **Patent No.: US 6,416,808 B1**
(45) **Date of Patent: Jul. 9, 2002**

(54) **METHOD OF OBTAINING A HYDROXYTYROSOL-RICH COMPOSITION FROM VEGETATION WATER**

(75) Inventor: **Roberto Crea**, San Mateo, CA (US)

(73) Assignee: **CreAgri, Inc.**, Hayward, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/944,744**

(22) Filed: **Aug. 31, 2001**

Related U.S. Application Data

(60) Provisional application No. 60/230,535, filed on Sep. 1, 2000.

(51) **Int. Cl.**[7] **A23D 7/00**; A61K 31/7048; A61K 31/05

(52) **U.S. Cl.** **426/601**; 514/27; 514/738

(58) **Field of Search** 514/738, 27; 426/601

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Primary Examiner—Phyllis G. Spivack
(74) *Attorney, Agent, or Firm*—Perkins Coie LLP; Peter J. Dehlinger; Larry W. Thrower

(57) **ABSTRACT**

The invention provides an olive-derived dietary supplement comprising hydroxytyrosol and oleoeuropein in specific weight ratios.

6 Claims, 5 Drawing Sheets

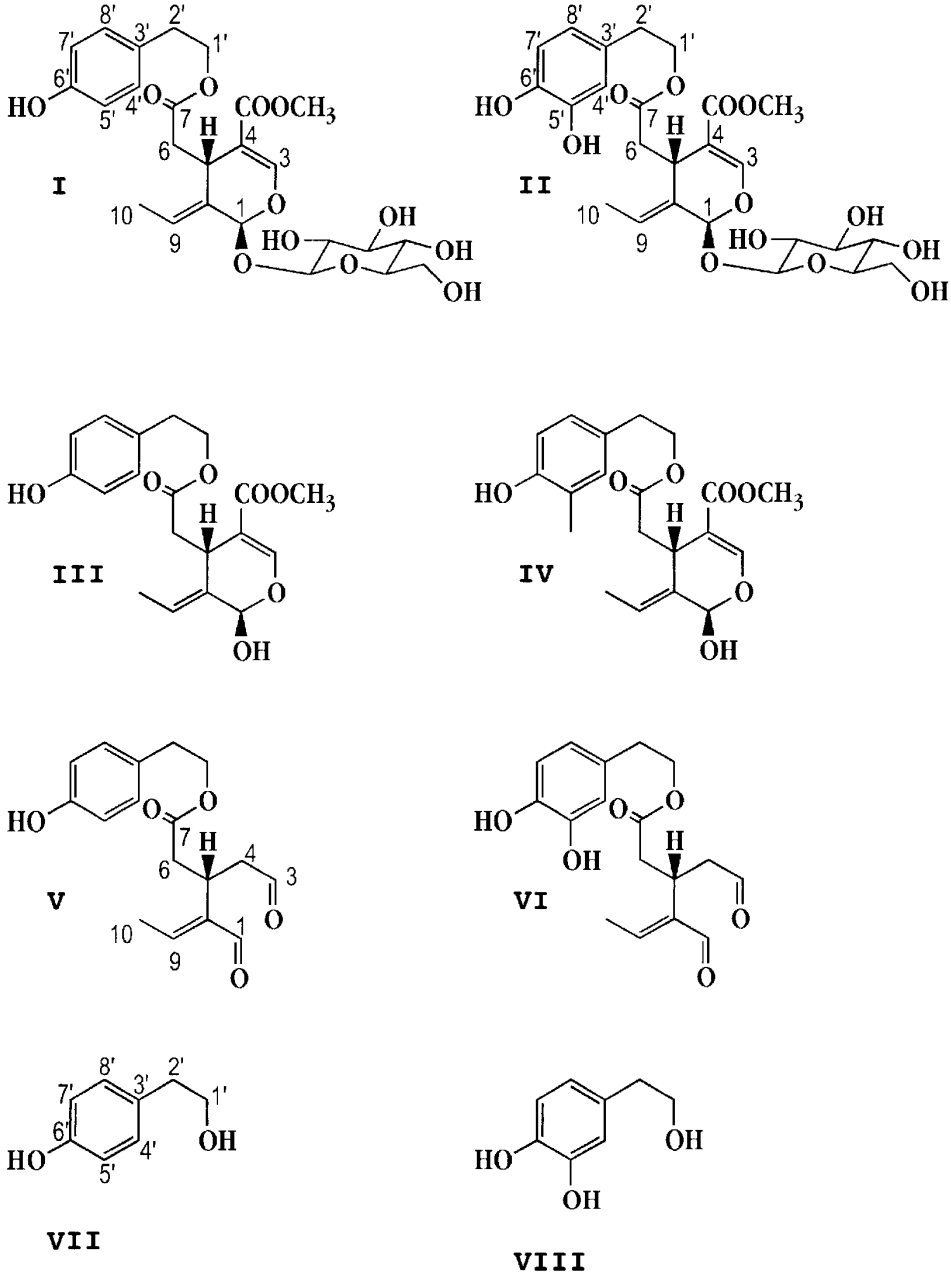

Fig. 1

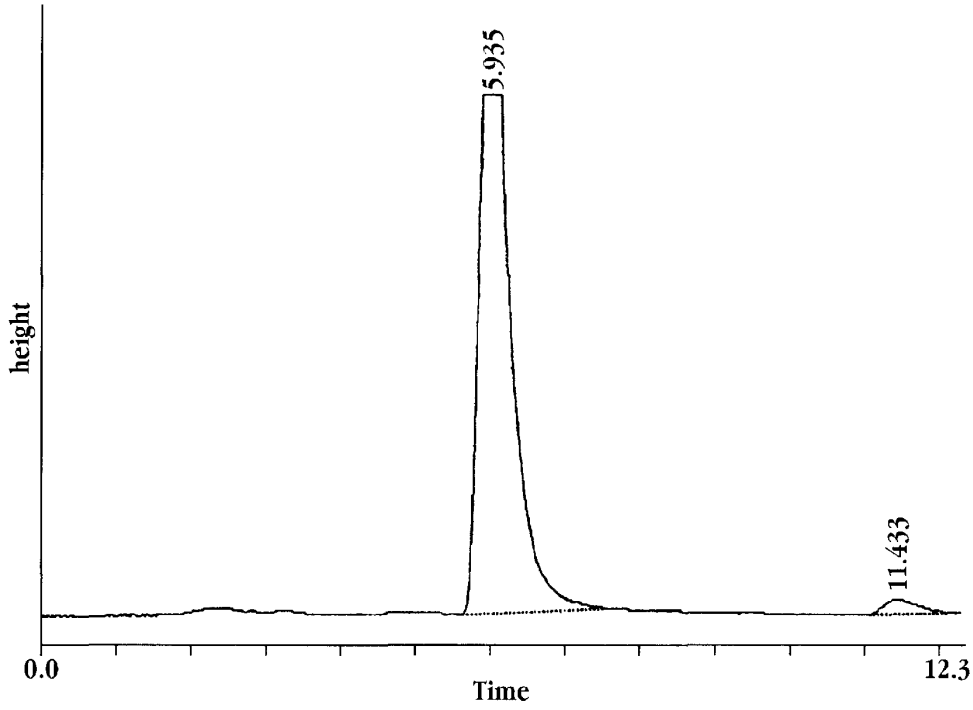

Fig. 2

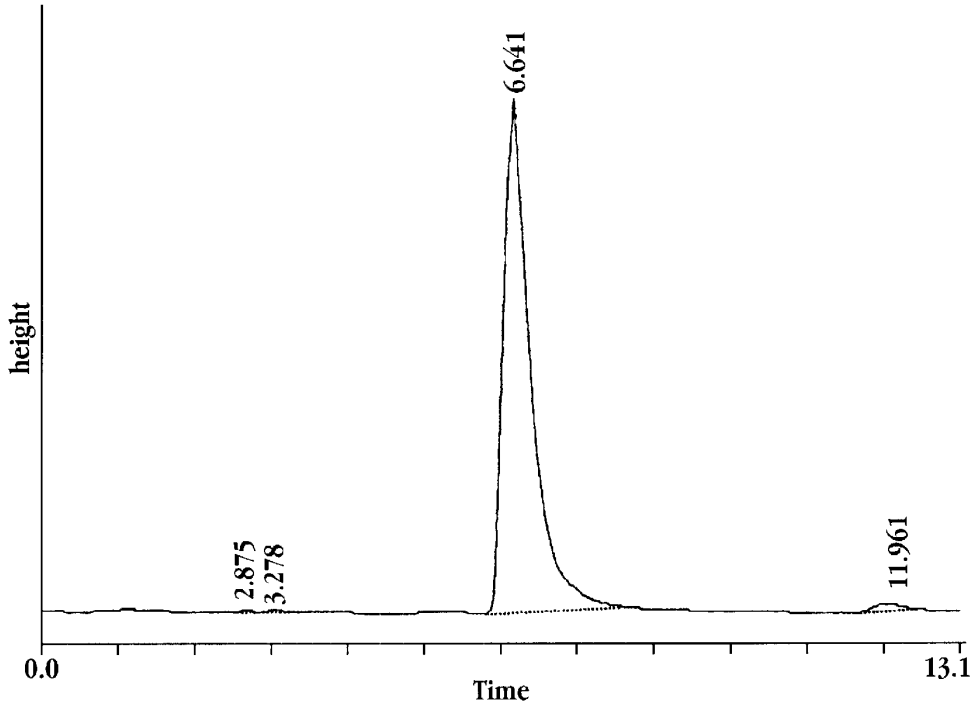

Fig. 3

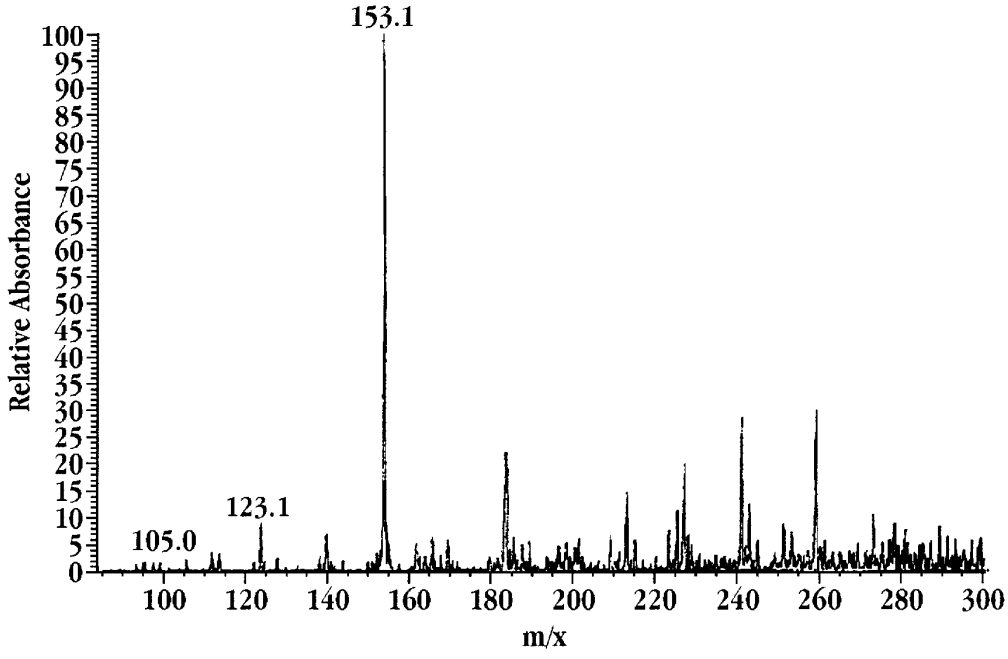
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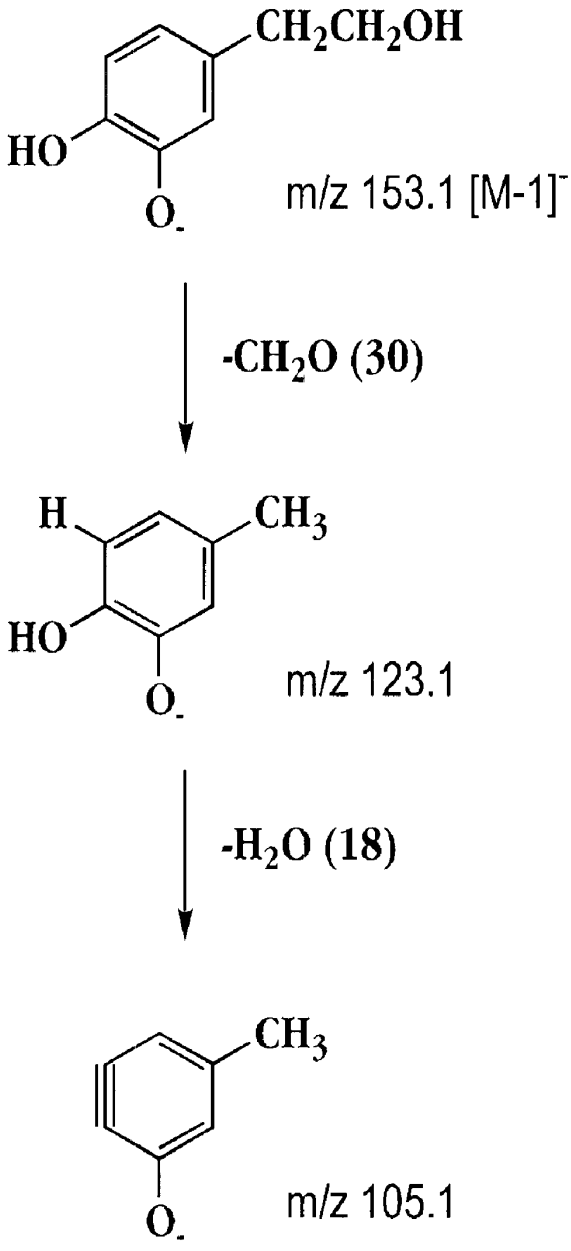
Fig. 4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-H2O (18)
CH3
O.
m/z 105.1

Fig. 5

METHOD OF OBTAINING A HYDROXYTYROSOL-RICH COMPOSITION FROM VEGETATION WATER

This application claims the benefit of U.S. Provisional Application No. 60/230,535 filed Sep. 1, 2000, which is expressly incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

This invention relates to a phenolic fraction of a group of compounds present in olive plants known as hydroxytyrosol (3,4-dihydroxyphenylethanol). Particularly, the invention provides an olive extract containing hydroxytyrosol, with low amounts or substantially free of oleoeuropein and tyrosol, and a method of obtaining the same.

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BACKGROUND OF THE INVENTION

A high amount of dietary fat has been implicated in the development of several diseases (Owen et al., 2000c). Atherosclerosis (Kuller, 1997) and coronary heart disease (Gerber, 1994), as well as cancer of the breast (La Vecchia et al., 1998), prostate (Chan et al., 1998), ovary (Risch et al., 1994), and colon (Armstrong and Doll, 1975) have each been associated with elevated dietary fat. However, evidence indicates that it is not only the amount, but also the type of dietary fat that is important in the etiology of some cancers (Bartsch et al., 1999).

Olive oil, the principal fat component of the Mediterranean diet, has been associated with a lower incidence of coronary heart disease (Owen et al., 2000b; Parthasarathy et al., 1990; Mattson and Grundy, 1985) and certain cancers (d'Amicis and Farchi, 1999; Braga et al., 1998; Martin-Moreno et al., 1994). Several laboratories have reported that the hydrolysis of the olive oil phenolics oleuropin and other family members lead to small phenolic components with strong chemoprotective activity (Owen et al., 2000a; Manna et al., 2000). In particular, the olive oil phenolic hydroxytyrosol prevents low density lipoprotein (LDL) oxidation (Visioli and Galli, 1998), platelet aggregation (Petroni et al., 1995), and inhibits 5- and 12-lipoxygenases (de la Puerta et al., 1999; Kohyama et al., 1997). Hydroxytyrosol has also been found to exert an inhibitory effect on peroxynitrite dependent DNA base modification and tyrosine nitration (Deiana et al., 1999), and it counteracts cytotoxicity induced by reactive oxygen species in various human cellular systems (Manna et al., 2000). Finally, studies have shown that hydroxytyrosol is dose-dependently absorbed in humans following ingestion, indicating its bioavailability (Visioli et al, 2000).

Conventionally, olive oil production involves crushing olives, including the pits, to produce a thick paste. During this procedure, the crushed olives are continuously washed with water, a process known as "malaxation." The paste is then mechanically pressed to squeeze out the oil content. In addition to providing olive oil, the pressing also squeezes out the paste's water content. Such washing and pressing steps yield a considerable amount of water, referred to as "vegetation water."

Both the pit and the pulp of olives are rich in water-soluble, phenolic compounds. Such compounds are extracted from olives during malaxation, according to their partition coefficients, and end up in the vegetation water. This explains why various phenolic compounds, such as oleoeuropein and its derivatives, produced in olive pulp, can be found in abundance in vegetation waters. Similarly, a number of monophenolic compounds, such as tyrosol and its derivatives, produced in olive pits, are also abundant in vegetation waters.

Because of the strong chemoprotective activity of hydroxytyrosol, it is desirable to develop a method which produces an aqueous olive extract with a high percentage of hydroxytyrosol.

SUMMARY OF THE INVENTION

In one aspect, the invention includes a method of producing a hydroxytyrosol-rich composition. The method has the steps of (a) producing vegetation water from olives, preferably depitted olive meat, (b) adding acid to the vegetation water in an amount effective to produce a pH between 1 and 5, preferably 2–4, and (c) incubating the acidified vegetation water for a period of at least two months, typically 6–12 months until at least 75%, and preferably at least 90% of the oleoeuropein originally present in the vegetation water has been converted to hydroxytyrosol.

In one embodiment, the incubating is carried out until the vegetation water has a weight ratio of hydroxytyrosol to oleoeuropein of between 5:1 and 200:1, preferably 10:1 and 100:1. In a related embodiment, the incubating is carried out until the vegetation water has a weight ratio of hydroxytyrosol and tyrosol of between 3:1 and 50:1, typically 5:1 to 30:1.

The method may further include fractionating the incubated, vegetation water to separate hydroxytyrosol from other components, and/or drying the vegetation water of isolated hydroxytyrosol to produce a dried extract.

In another aspect, the invention includes a method of producing a hydroxytyrosol-rich composition that includes the steps of (a) producing vegetation water from olives; (b) optionally, drying the vegetation water; (c) contacting the optionally dried vegetation water with a supercritical fluid; and (d) recovering the hydroxytyrosol-rich composition from the contacted vegetation water. In one embodiment, the hydroxytyrosol-rich composition includes at least about 95 percent by weight hydroxytyrosol. In another embodiment, the hydroxytyrosol-rich composition includes at least about 97 percent by weight hydroxytyrosol. In yet another embodiment, the hydroxytyrosol-rich composition includes at least about 99 percent by weight hydroxytyrosol.

In one embodiment, the recovering step described above includes the steps of (a) recovering the supercritical fluid, where the supercritical fluid contains the hydroxytyrosol; and (b) vaporizing the supercritical fluid to extract the hydroxytyrosol-rich composition. In another embodiment, the contacting step described above comprises the steps of (a) providing a porous membrane having opposite sides in a module under pressure with the membrane serving as a barrier interface between a fluid and a dense gas, the membrane being nonselective for said hydroxytyrosol; (b) providing the supercritical fluid into the module on one side of the membrane and the vegetation water on the opposite side of the membrane; (c) and extracting the hydroxytyrosol across the membrane as driven by a concentration gradient of the hydroxytyrosol between the vegetation water and the supercritical fluid. In one embodiment, the porous membrane is a hollow fiber membrane. In another embodiment, the supercritical fluid is carbon dioxide.

In another aspect, the invention includes a dietary supplement comprising an aqueous extract of olives containing a weight ratio of hydroxytyrosol to oleoeuropein of between 5:1 and 200:1, typically 10:1 and 100:1.

In a related aspect the invention includes a dietary supplement comprising an aqueous extract of olives containing a weight ratio of hydroxytyrosol and tyrosol of between 3:1 and 50:1, typically 5:1 and 30:1.

The above supplements may be dried to provide a powder extract, which can formulated into a tablet, capsule, pill, or confection food additive.

These and other objects and features of the invention will be more fully appreciated when the following detailed description of the invention is read in conjunction with the accompanying figure and tables.

BRIEF DESCRIPTION OF FIGURES

FIG. **1** shows the structures of phenolic compounds and their precursors detected in olive oil: ligstroside (I); oleuropein glucoside (II); aglycone of ligstroside (III); aglycone of oleuropein glucoside (IV); dialdehydic form of ligstroside aglycone lacking a carboxymethyl group (V); dialdehydic form of oleuropein glucoside aglycone lacking a carboxymethyl group (VI); tyrosol (VII); hydroxytyrosol (VIII).

FIG. **2** shows the HPLC analysis of a hydroxytyrosol-rich composition of the invention after supercritical carbon dioxide extraction from vegetation water.

FIG. **3** shows the HPLC analysis of a hydroxytyrosol-rich composition of the invention following supercritical carbon dioxide extraction, with synthetic hydroxytyrosol.

FIG. **4** shows the mass spectrum of a hydroxytyrosol-rich composition of the invention.

FIG. **5** illustrates the fragmentation pathway of hydroxytyrosol.

DETAILED DESCRIPTION OF THE INVENTION

I. Definitions

Unless otherwise indicated, all terms used herein have the same meaning as they would to one skilled in the art of the present invention. It is to be understood that this invention is not limited to the particular methodology, protocols, and reagents described, as these may vary.

By "oleoeuropein" is intended secoiridoid glucoside oleuropein (Structure II in FIG. **1**).

By "tyrosol" is intended 4-hydroxyphenethyl alcohol (Structure VII in FIG. **1**).

By "hydroxytyrosol" is intended 3,4-dihydroxyphenethyl alcohol (Structure VIII in the FIG. **1**).

II. Method of the Invention

The invention provides, in one aspect, provides a hydroxytyrosol-rich composition from olive-derived vegetation water. It has been discovered that under specific conditions, as described below, hydroxytyrosol may be obtained from the vegetation water of olives. Considered below are the steps in practicing the invention.

A. Producing Vegetation Water

The method of the invention employs olives that may be obtained from conventional and commercially available sources such as growers. Preferably, the vegetation water is obtained from pitted olives. The olives processed according to the method disclosed herein may be pitted by any suitable means. Pits in the olives contain tyrosol which is an undesired component in the vegetation water and which may not be appreciably broken down by the acid treatment described below. The pits may be separated from the pulp manually or in an automated manner as described below. Preferably, such means should be capable of segregating the pits without breaking them, which might otherwise cause higher concentrations of tyrosol in the vegetation water. In another embodiment, hydroxytyrosol is extracted from vegetation water obtained from olives that have not been pitted.

To produce vegetation water, olive pulp from the olives is first pressed to obtain a liquid-phase mixture including olive oil, vegetation water, and solid by-products. Thereafter, the vegetation water is separated from the rest of the liquid phase mixture and collected. Exemplary methods of obtaining vegetation water are described in co-owned U.S. Pat. Nos. 6,165,475 and 6,197,308, both to R. Crea, each of which are expressly incorporated herein by reference in their entirety.

For purposes of commercial production, it may be desirable to automate various aspects of the invention. In this regard, one embodiment contemplates the use of an apparatus as disclosed in U.S. Pat. Nos. 4,452,744, 4,522,119 and 4,370,274, each to Finch et al., and each expressly incorporated herein by reference. Briefly, Finch et al. teach an

apparatus for recovering olive oil from olives. Initially, olives are fed to a pulper that separates the olive pits from the olives to obtain a pitless olive meat. The meat is then taken up by an extraction screw that subjects the meat to an extraction pressure sufficient to withdraw a liquid phase, comprising oil, water and a minor proportion of olive pulp. The liquid phase is collected in a bin and then sent to a clarifying centrifuge that separates the pulp from the liquid phase to obtain a mixture comprising olive oil and vegetation water. A purifying centrifuge then separates the vegetation water and a small proportion of solid matter from the mixture to obtain an olive oil, substantially free of vegetation water, that is collected in a tank. According to Finch et al., the water is put to a disposal means such as a sewer. The present invention, in sharp contrast, provides for the collection, saving and use of the vegetation water to extract hydroxytyrosol.

Additional devices that may be used in practicing the present invention are disclosed in Italian Pat. Nos. 1276576 and 1278025, each of which is expressly incorporated herein by reference. As above, these devices can be used to separate the pulp from the pits prior to processing of the crushed olive pulp into oil, water, and solid residues.

B. Conversion of Oleoeuropein to Hydroxytyrosol

In one aspect of the invention, the oleoeuropein contained in the vegetation water is converted to hydroxytyrosol. The pH of the vegetation water may be decreased by the addition of acid, and the vegetation water allowed to incubate under conditions which, according to the discovery of the invention, promote acid hydrolysis of oleoeuropein to hydroxytyrosol. The sample may then be fractionated to separate hydroxytyrosol from other compounds.

In a preferred embodiment, the added acid is citric acid. The acid is added to the vegetation water to adjust the pH to 1–5, preferably 2–4. Solid citric acid can be added while continuously stirring in an amount of preferably about 25 to 50 pounds of acid per about 1000 gallons of vegetation water. The pH of the resulting solution can be monitored, and further addition of acid may be necessary to achieve the desired pH. Exemplary methods showing the conversion of oleoeuropein to hydroxytyrosol following the addition of citric acid are given in Examples 1 and 2.

The acid may also be an organic or inorganic acid other than citric acid. Exemplary acids which may be used in the present invention include the inorganic substances known as the mineral acids—sulfuric, nitric, hydrochloric, and phosphoric acids—and the organic compounds belonging to the carboxylic acid, sulfonic acid, and phenol groups. The addition of acid to the vegetation water serves several purposes: (i) it stabilizes the vegetation water; (ii) it prevents fermentation of the vegetation water; and (iii) it slowly hydrolizes the oleouropein, converting it to hydroxytyrosol, as shown in Examples 1 and 2. Tables 1 and 2, in Examples 1 and 2, respectively, contain data from two samples of vegetation water and the respective percent composition of various components in the samples over time following the addition of citric acid. In one embodiment, the mixture is allowed to incubate until hydroxytyrosol is 75–90% of the total combination of tyrosol and hydroxytyrosol, and substantially none of the oleoeuropein in the original mixture remains.

C. Purification of Hydroxytyrosol

Following the conversion of oleouropein to hydroxytyrosol, the incubated vegetation water may be fractionated by a number of methods known in the art. Alternatively, vegetation water may be fractionated prior to treatment with acid. Exemplary methods of fractionating include partitioning with an organic solvent, high pressure liquid chromatography (HPLC), or supercritical fluids.

Vegetation water obtained as described above provides a solution which is rich in low molecular weight polyphenols, particularly hydroxytyrosol and a small amount of tyrosol. The concentration of hydroxytyrosol in the processed water may range from 4–5 grams per liter to 10–15 grams per liter depending upon the degree of dilution during the olive oil extraction. In one embodiment, the invention provides a method of extraction or purification that selectively enriches the content of hydroxytyrosol without the addition of contaminants. Thus, the major polyphenolic component, hydroxytyrosol, is isolated from other members of the polyphenolic family, impurities, suspended solids, tannins, and other molecules contained in the vegetation water. Hydroxytyrosol may therefore be produced in a purity and quantity not readily available by current synthetic or natural extraction methods.

A supercritical fluid is a gas that becomes very dense above its critical temperature and pressure. Its properties are between those of a gas and liquid, resulting in increased ability to dissolve compounds. Its relatively high density, high diffusivity, and low viscosity allow it to extract compounds faster than conventional liquid solvents. Carbon dioxide is the gas used most widely for supercritical fluid processing of foods and food ingredients because it is natural, nontoxic, non-flammable, and relatively inert and leaves no residue in the extracted product. Typical liquid extraction with supercritical carbon dioxide is usually done by dispersing one phase in the other in large contacting columns or towers, where the solute containing fluid, such as juices, flows downward by gravity, and the supercritical carbon dioxide flows upward. Mass transfer occurs at the interface between the two phases.

Alternatively, continuous extraction of liquids and suspensions can be achieved using supercritical fluids, such as carbon dioxide, and porous membranes instead of contacting columns. Instead of dispersing the phases, the liquid is fed continuously through porous polypropylene membranes configured as hollow fiber bundles or spiral wound sheets. The liquid passes through the porous membranes within a pressurized module, while supercritical carbon dioxide flows countercurrently on the other side of the membrane. The pressure in the module is essentially the same, so that the extraction is driven by the concentration gradient between the fluid and the supercritical carbon dioxide. The extract may be recovered by vaporizing the carbon dioxide for recycling. An exemplary method of extraction using supercritical carbon dioxide and porous membranes is described in U.S. Pat. No 5,490,884, which is expressly incorporated by reference herein in its entirety.

Other supercritical fluids, instead of, or in combination with, carbon dioxide. These fluids include methane, ethane, propane, butane, isobutane, ethene, propene, hydrofluorocarbons, tetrafluoromethane, chlorodifluoromethane, carbon dioxide, dinitrogen monoxide, sulphur hexafluoride, ammonia, and methyl chloride.

Example 3 describes a small scale experiment in support of the invention, wherein hydroxytyrosol was isolated from vegetation water using supercritical carbon dioxide and porous membranes. HPLC and mass spectrometry analysis of the isolated hydroxytyrosol shows the sample to be 97–99% pure hydroxytyrosol. Thus, the invention provides a hydroxytyrosol-rich composition containing at least about 80% hydroxytyrosol, preferably at least about 90% hydroxytyrosol, more preferably at least about 95%

hydroxytyrosol, even more preferably at least about 97% hydroxytyrosol, and yet, even more preferably at least about 99% hydroxytyrosol.

Prior to extraction with a supercritical fluid the vegetation water may have carriers, which are known to those of skill in the art, such as maltodextran and/or polypropylene beads, added to the solution; and/or the solution may be dried. The drying step preferably removes at least about 90%, more preferably at least about 95%, and even more preferably at least about 98% of the water from the vegetation water.

An important feature of membrane reactors is the fact that contact surface interfacial area can be added independently of fluid velocities. Accordingly, the invention contemplates a large scale unit where the surface membrane area of the membrane used for extraction is at least about 100 square yards, preferably at least about 300 square yards, and even more preferably at least about 600 square yards to allow separation of hydroxytyrosol from large volumes of vegetation water. Thus, the membrane system of the invention would, in one aspect, be able to accommodate a flow rate of between 1–20 liters per minute, preferably between 5–10 liters per minute.

Additional purification methods may also be used in accordance with the invention as mentioned above. HPLC isolation of hydroxytyrosine is described in: Ficarra et al., 1991; Romani et al., 1999; and Tsimidou, 1992, each of which is expressly incorporated by reference herein.

III. Hydroxytyrosol-Rich Dietary Supplement

It should be appreciated that hydroxytyrosol produced by the method described above may be used for a variety of applications. For example, hydroxytyrosol obtained by the method of the present invention can be used: (i) as a natural anti-bacterial, anti-viral and/or fungicidal product for agricultural and/or pest control applications, and (ii) as a therapeutic and/or an anti-oxidant for a variety of health purposes. In one exemplary embodiment, the hydroxytyrosol, is administered to a mammalian subject, such as a person desirous of one or more of the benefits associated with hydroxytyrosol.

The hydroxytyrosol obtained by the method of the invention can be administered orally or parenterally. Oral dosage forms can be in a solid or liquid form. Such dosage forms can be formulated from purified hydroxytyrosol or they can be formulated from aqueous or aqueous-alcoholic extracts. Regarding the latter, aqueous or aqueous-alcoholic (e.g., water-methanol or water-ethanol) extracts can be spray-dried to provide a dry powder that can be formulated into oral dosage forms with other pharmaceutically acceptable carriers. The aqueous or aqueous-alcoholic extracts can be formulated to contain various weight ratios of hydroxytyrosol to oleoeuropein of between 5:1 and 200:1, preferably between about 10:1 and about 100:1. The extracts may also be formulated to contain various weight ratios of hydroxytysol and tyrosol of between about 3:1 and about 50:1, preferably between about 5:1 and about 30:1.

The solid oral dosage form compositions in accordance with this invention are prepared in a manner well known in the pharmaceutical arts, and comprise hydroxytyrosol in combination with at least one pharmaceutically acceptable carrier. In making such compositions, a hydroxytyrosol-rich composition, either in substantially pure form or as a component of a raw distillate or extract, is usually mixed, diluted or enclosed with a carrier. The carrier can be in a solid form, semi-solid or liquid material which acts as a vehicle, carrier or medium for the active ingredient. Alternatively, the carrier can be in the form of a capsule or other container to facilitate oral administration. Thus, the solid oral dosage forms for administration in accordance with the present invention can be in the form of tablets, pills, powders or soft or hard gelatin capsules.

Alternatively, the hydroxytyrosol obtained in accordance with this invention for oral administration can be in liquid form wherein the pharmaceutically acceptable carrier is water or an aqueous-alcoholic medium.

The compositions for administration in the present invention can also be formulated with other common pharmaceutically acceptable excipients, including lactose, dextrose, sucrose, sorbitol, mannitol, starches, gums, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, methylcellulose, water, alcohol and the like. The formulations can additionally include lubricating agents such as talc, magnesium stearate and mineral oil, wetting agents, emulsifying and suspending agents, preserving agents such as methyl- and propylhydroxybenzoates, sweetening agents or flavoring agents. Further, the compositions of the present invention can be formulated so as to provide quick, sustained or delayed release of the active ingredient after administration to a subject.

Parenteral formulations for use in accordance with the present invention are prepared using standard techniques in the art. They are commonly prepared as sterile injectable solutions, using a parenterally acceptable carrier such as isotonic saline solution or as a sterile packaged powder prepared for reconstitution with sterile buffer or isotonic saline prior to administration to a subject.

From the foregoing, it can be seen how various objects and features of the invention are met. Those skilled in the art can now appreciate from the foregoing description that the broad teachings of the present invention can be implemented in a variety of forms. Therefore, while this invention has been described in connection with particular embodiments and examples thereof, the true scope of the invention should not be so limited. Various changes and modification may be made without departing from the scope of the invention, as defined by the appended claims.

The following examples illustrate methods of producing hydroxytyrosol-rich compositions in accordance with the invention. The examples are intended to illustrate, but in no way limit, the scope f the invention.

EXAMPLES

Example 1

Conversion from Oleoeuropein to Hydroxytyrosol Following the Addition of About 25 Pounds of Citric Acid/1000 Gallons

Table 1 shows the conversion of oleoeuropein to hydroxytyrosol over time following the addition of about 25 pounds of citric acid per 1000 gallons of vegetation water. The percentages in Table 1 are shown as weight percentages of the total phenolic compounds in the solution. As demonstrated in Table 1, hydroxytyrosol comprises over 80% of the phenolic compounds in the solution after 12 months.

TABLE 1

Conversion from Oleoeuropein to Hydroxytyrosol Following the Addition of About 25 Pounds of Citric Acid/1000 Gallons

Component	Composition at T = 2 mo.	Composition at T = 3 mo.	Composition at T = 4.5 mo.	Composition at T = 12 mo.
Hydroxytyrosol	30.4%	32%	48.4%	80.2%
Tyrosol	2.5%	5%	2.2%	3.6%
Oleoeuropein	41%	36.6%	25.1%	1.2%
Oleoeuropein aglycone	4.2%	4.6%	2.7%	3.7%

Example 2

Conversion from Oleoeuropein to Hydroxytyrosol Following the Addition of About 50 Pounds of Acid/1000 Gallons

Table 2 shows the conversion of oleoeuropein to hydroxytyrosol over time following the addition of about 50 pounds of citric acid per 1000 gallons of vegetation water. The percentages in Table 2 are shown as weight percentages of the total phenolic compounds in the solution. Significantly, as demonstrated in Table 2, hydroxytyrosol comprises over 45% of the phenolic compounds in the solution after 2 months.

TABLE 2

Conversion from Oleoeuropein to Hydroxytyrosol Following the Addition of About 50 Pounds of Acid 1000 Gallons

Component	Composition at T = 2 mo.	Composition at T = 12 mo.
Hydroxytyrosol	45.7%	78.5%
Tyrosol	2.9%	3.3%
Oleoeuropein	28.7%	1.5%
Oleoeuropein aglycone	4.1%	3.5%

Example 3

Extraction of Hydroxytyrosol from Vegetation Water

An aliquot (0.5 ml) of vegetation water containing about 40 mg of dry solid (maltodextran) was mixed with polypropylene porous beads and dried. The dry mix was used for extraction with supercritical carbon dioxide (PoroCrit, LLC, Berkeley, Calif.). The collected sample (about 2.0 mg) was analyzed by HPLC. The profile of the sample is shown in FIG. **2**, and Table 3 shows the area under the major peak to be 97%. When synthetic hydroxytyrosol was added to the sample and analyzed by HPLC, one major peak appeared, as shown in FIG. **3**, indicating that the major product of the sample is hydroxytyrosol (Table 4).

Mass spectrometry analysis of the sample, as shown in FIG. **4**, confirmed that the major product is hydroxytyrosol. The sample was diluted to a final concentration of 26 micrograms per milliliter with methanol and analyzed in negative ionization mode on a Finnigan LCQ fitted with an ESI probe. The infusion was at 3 microliters per minute using an integrated syringe pump. The temperature was 270 C, needle voltage +4.2 V, sheath gas 45 units, and auxiliary gas 10 units. The fragmentation pathway of hydroxytyrosol is shown in FIG. **5**. As can be seen in FIG. **4**, hydroxytyrosol (mass/charge 153.1) and its fragmentation products (123.1 and 105.1 mass/charge) account for the majority of the product abundance in the multi-stage spectrum.

TABLE 3

Peak Analysis of FIG. 2 HPLC Results

Peak No.	Time	Height (μV)	Area (μV-sec)	Area (%)
1	5.935	215542	6687705	97.476
2	11.433	5686	173104	2.523

TABLE 4

Peak Analysis of FIG. 3 HPLC Results

Peak No.	Time	Height (μV)	Area (μV-sec)	Area (%)
1	2.875	1345	13895	0.26
2	3.278	1076	14140	0.265
3	6.641	211204	5241105	98.240
4	11.961	2587	65811	1.233

It is claimed:

1. A dietary supplement comprising an aqueous extract of olives containing a weight ratio of hydroxytyrosol to oleoeuropein of between about 5:1 and about 200:1.

2. The supplement of claim **1**, which has a weight ratio of hydroxytyrosol to oleoeuropein of between about 10:1 and about 100:1.

3. The dietary supplement of claim **1**, wherein said supplement is dried to provide a powder extract.

4. The dietary supplement of claim **1**, wherein said extract is in the form of a tablet, capsule, pill, or confection food additive.

5. A dietary supplement comprising an aqueous extract of olives containing a weight ratio of hydroxytyrosol and tyrosol of between about 3:1 and about 50:1.

6. The dietary supplement of claim **5**, containing a weight ratio of hydroxytyrosol and tyrosol of between about 5:1 and about 30:1.

* * * * *

(12) **United States Patent**
Crea

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(45) **Date of Patent: Jul. 10, 2012**

(54) **METHOD FOR TREATMENT OF INFLAMMATION**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 731 days.

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(58) **Field of Classification Search** ..... None
See application file for complete search history.

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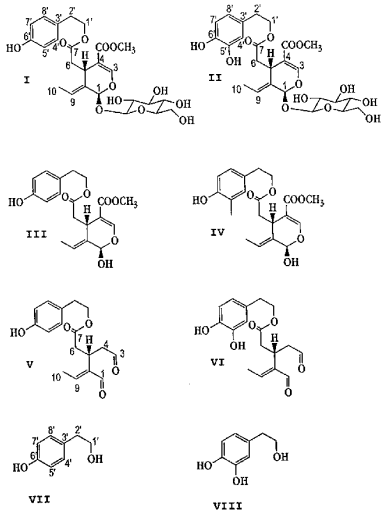
(57) **ABSTRACT**

A method of treating inflammation, an inflammatory condition, or AIDS-associated neurological disorder in a subject in need of such treatment is disclosed. The method includes administering to said subject a pharmaceutically effective amount of substantially purified hydroxytyrosol or a substantially purified mixture of hydroxytyrosol and oleuropein. Also disclosed are compositions for use in practicing the method.

16 Claims, 1 Drawing Sheet



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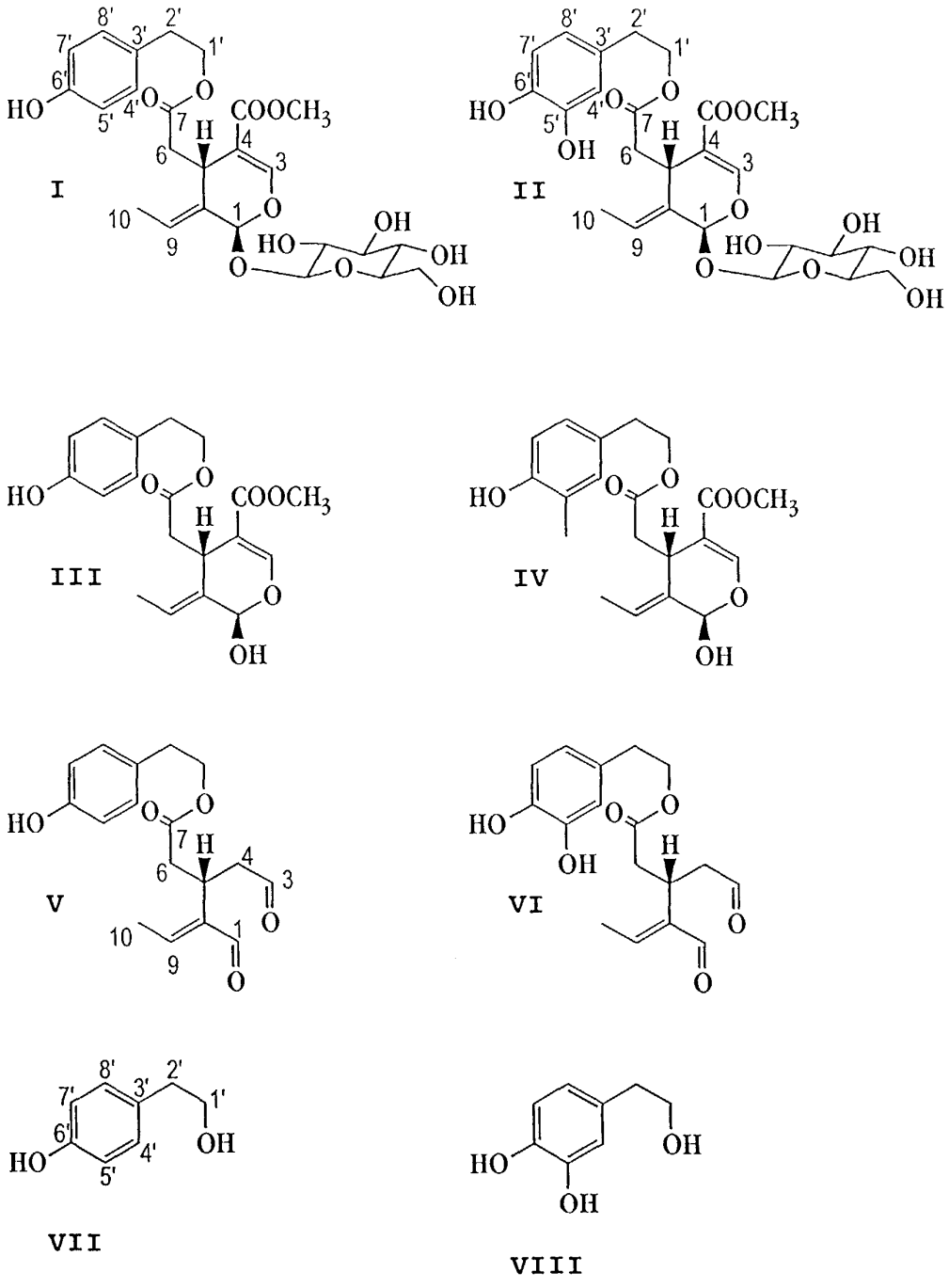

Fig. 1

METHOD FOR TREATMENT OF INFLAMMATION

This application claims the priority benefit of U.S. Provisional Application No. 60/356,847, filed Feb. 13, 2002, which is incorporated herein in its entirety by reference.

FIELD OF THE INVENTION

The present invention relates to methods for treating AIDS-associated neurological disorders, inflammation and inflammation-associated disorders and to pharmaceutical compositions for use in practicing the method.

BACKGROUND OF THE INVENTION

The Acquired Immunodeficiency Syndrome (AIDS), caused by the human immunodeficiency virus type-1 (HIV-1), is one of the ten leading causes of death in the world (Koutsilieri, 2001). According to a June 2000 World Health Organization (WHO) report on global human immunodeficiency virus (HIV)/AIDS pandemic, nearly 35 million adults and 2 million children worldwide are infected with HIV and it is estimated that one third of the adults and more than one half of the children will develop a dementing illness.

This virus, transmitted by sexual contact or exposure to infected blood products, has to this point eluded attempts at eradication and continues to spread through human populations in both industrialized and non-industrialized nations. Although modern anti-viral medications may control viral replication and prolong life, there is currently no preventative vaccine and no examples of a cure (Glass, 2001).

A variety of neurological syndromes occur throughout the course of HIV infection, affecting the central nervous system, peripheral nervous system, and muscle. The sequelae of HIV infection can be categorized as either related to opportunistic infections of the nervous system, or as direct or indirect effects of the virus itself. Some disorders are manifested early and some late during the infectious process, and the pathological changes include inflammatory, demyelinating, and degenerative changes. This spectrum of diseases associated with a single virus infection is unique in virology.

Neurological disease occurs rarely at the time of initial infection with HIV, even before seroconversion, and prior to the profound immunosuppression of the latter stages of HIV infection. These early manifestations include aseptic meningitis or encephalitis, acute and chronic inflammatory demyelinating polyneuropathies, mononeuritis multiplex associated with peripheral nerve vasculitis, and HIV-associated polymyositis (McArthur, 1987).

Oxidative stress has been implicated in a variety of diseases and pathological conditions, including endothelial cell cytotoxicity, cancer, and coronary heart diseases, such as thrombosis and hyperlipemia (Addis, 1995). Recent studies have shown that elevated lipid peroxidation levels (oxidative stress) may play a role in the pathogenesis of Alzheimer's disease which includes a group of neurodegenerative disorders with diverse etiologies, but the same hallmark brain lesions (Practico, 1998).

Clinical studies have established that elevated plasma concentrations of LDL are associated with atherosclerosis, a most prevalent cardiovascular disease and the principle cause of heart attack, stroke and vascular circulation problems (Sarkkinen, 1993). It is believed that a reduction of atherogenic lipid peroxides, which are transported in the LDL fraction of blood serum, can reduce the risk of atherogenesis (Mazur, 1999). Antioxidants limit oxidative modification of

LDL and consequently lower plasma concentrations of LDL, thereby acting as anti-atherogenic compounds (Sarkkinen, 1993). The oxidation of LDL has been reported as a model for testing the ability of polyphenols to act as antioxidants by breaking the peroxidative cascade described above (Rice-Evans, 1995).

A safe, relatively inexpensive, orally administered neuro protectant that reduces the sequelae of cerebral oxidative stress in the setting of HIV-associated brain disease would have great value as an adjunctive therapy. Benefits include those based on evidence regarding the effect of free-radical damage of oxidative stress on key organ systems. They include cerebral antioxidant activity with reduction of ongoing brain injury (Shi 1998; Treitinger 2000); antiviral effects (oxidative stress activates a transcription factor necessary for HIV replication, and phenols are effective in vitro against HIV-1: Ng, 1997); and antiatherosclerotic cardiovascular benefits. Of note, cardiovascular risk has become a concerning issue among HAART-treated individuals as the incidence of severe hyperlipidemia has increased (Lipodystrophy Syndrome). Oxidative stress inhibits the key enzyme responsible for the transfer and metabolism of cell-derived cholesterol via HDL. Antioxidant therapy increases the capacity of HDL for cholesterol uptake, and could lower cholesterol. In addition, antioxidants have been shown in vitro and in vivo to decrease oxidized LDL, strongly implicated as a mediator of endothelial damage of cardiovascular disease (Caruso 1999, Napoli 2001).

SUMMARY OF THE INVENTION

Accordingly, it is an object of the invention to provide, in one aspect, a method for treating an AIDS-associated neurological disorder in a subject in need of such treatment. The method includes administering to the subject a pharmaceutically effective amount of a treatment agent having hydroxytyrosol and oleuropein. In one embodiment, the weight ratio of hydroxytyrosol to oleuropein of between about 1:1 and about 200:1. In another embodiment, the weight ratio is between about 5:1 and about 100:1. In yet another embodiment, the weight ratio of hydroxytyrosol and oleuropein is between about 10:1 and about 50:1.

In a preferred embodiment, the treatment agent is prepared by a process comprising the steps of producing vegetation water from olives, adding acid to the vegetation water in an amount effective to produce a pH between about 1 and about 5, and incubating the acidified vegetation water until at least 75% of oleuropein originally present in the vegetation water has been converted to hydroxytyrosol.

An exemplary disorder for treatment is AIDS dementia. A preferred route of administration includes oral delivery.

In one embodiment, the administering further includes administering a second disease treatment agent. Administering the second treatment agent may be before or after administration of the first treatment agent. Alternatively, administering the second treatment agent is coincident with administering the first treatment agent. Preferably the second treatment agent is an antiretroviral agent.

In another embodiment, the first agent is administered at a dosage of between about 0.1 mg/kg and 2000 mg/kg per day. Preferably, the first agent is administered at a dosage of between about 0.3 mg/kg and 1 mg/kg per day. Even more preferably, the agent is administered at a dosage of about 0.6 mg/kg per day.

In one embodiment, the subject is a human. In another embodiment, the agent is dried to provide a powder extract. In yet another embodiment, the agent is in the form of a tablet, capsule, or pill.

In another aspect, the invention contemplates a method of treating an AIDS-associated neurological disorder in a subject in need of such treatment. The method includes administering to said subject a pharmaceutically effective amount of substantially purified hydroxytyrosol or a substantially purified mixture of hydroxytyrosol and oleuropein.

Another aspect of the invention includes a method of treating a subject having an inflammatory condition characterized by a detectable clinical symptom or change in a level of a biochemical marker with respect to the normal range of the marker. The method includes administering to the subject a dose of an olive plant extract treatment agent. In one embodiment, the extract has a weight ratio of hydroxytyrosol to oleuropein of between about 1:1 and about 200:1. In another embodiment, the weight ratio is between about 5:1 and about 100:1. Preferably the weight ratio is between about 10:1 and about 50:1.

The method further includes continuing said administration until there is observed a return of the marker level to the normal range or a desired change in the clinical symptom. The marker or the clinical symptom may be (i) the symptoms and markers in joint pain and swelling in the case of joint inflammation; (ii) elevated levels of C-reactive protein in the case of coronary inflammation; (iii) respiratory distress in the case of bronchial inflammation; and/or (iv) elevated CSF levels of isoprostanes or functional or psychofunctional indicators in the case of neuro-inflammation.

In one embodiment, the marker is a cytokine such as tumor necrosis factor-α, interleukin-1, interleukin-6, and/or interleukin-8.

In another embodiment, the marker is corticotrophin, cortisol and/or prolactin.

In one embodiment, the inflammatory condition is selected from the group consisting of rheumatoid arthritis, osteoarthritis, and other inflammatory conditions involving acute joint inflammation, chronic joint inflammation, or both.

The extract may be prepared by a process that includes (a) producing vegetation water from olives; (b) adding acid to the vegetation water in an amount effective to produce a pH between about 1 and about 5; and (c) incubating the acidified vegetation water until at least 75% of oleuropein originally present in the vegetation water has been converted to hydroxytyrosol.

The administration may include a method selected from the group consisting of oral delivery, intramuscular injection, intravenous injection, transdermal delivery, and/or transmucosal delivery. Preferably the the administering includes oral delivery.

In one embodiment of the invention, the administering further comprises administering a second disease treatment agent. The administering of the second treatment agent may be before, after or coincident with administration of the first treatment agent. The second treatment agent includes one or more of the components selected from the group consisting of glucosamine sulfate, chondroitin sulfate, sea cucumber extract, hydrolyzed shark cartilage, collagen II, and methylsulfonylmethane.

In one embodiment of the invention the agent or extract is administered at a dosage of between about 0.1 mg/kg and 2000 mg/kg per day. Preferably the agent or extract is administered at a dosage of between about 0.3 mg/kg and 1 mg/kg per day. More preferably, the agent is administered at a dosage of about 0.6 mg/kg per day.

In one embodiment, the subject is a human.

In another embodiment, the agent is dried to provide a powder extract.

In yet another embodiment, the agent is in the form of a tablet, capsule, or pill. Alternatively, the agent may be in the form of a liquid or liquid drops.

In a broader aspect, the invention provides a method of treating an inflammatory condition in a subject in need of such treatment, comprising administering to said subject a pharmaceutically effective amount of substantially purified hydroxytyrosol or a substantially purified mixture of hydroxytyrosol and oleuropein. In one embodiment, the inflammatory condition is in response to a condition selected from the group consisting of delayed type hypersensitivity reaction, a symptom of psoriasis, an autoimmune disease, organ transplant, pain, fever, and tissue graft rejection. Preferably, the autoimmune disease is selected from the group consisting of: Reynaud's syndrome, autoimmune thyroiditis, EAE, multiple sclerosis and lupus erythematosus.

In another embodiment, the inflammatory condition is in response to a condition selected from the group consisting of adult respiratory distress syndrome (ARDS), multiple organ injury syndromes secondary to septicemia or trauma, reperfusion injury of myocardial or other tissues, acute glomerulonephritis, reactive arthritis, dermatoses with acute inflammatory components, acute purulent meningitis or other central nervous system inflammatory disorders, thermal injury, hemodialysis, leukapheresis, ulcerative colitis, Crohn's disease, necrotizing enterocolitis, granulocyte transfusion associated syndromes, and cytokine-induced toxicity.

In yet another embodiment, the inflammatory condition results from a condition selected from the group consisting of asthma, psoriasis, skin sunburn, inflammatory pelvic disease, inflammatory bowel disease, urethritis, uvitis, senusitis, pneumonitis, encephalitis, meningitis, myocarditis, nephritis, osteomyelitis, myositis, hepatitis, gastritis, enteritis, dermatitis, gingivitis, appendicitis, pancreatitis, cholocystitis and cholangititis.

In still another embodiment, the inflammatory condition is an acute inflammatory reaction. Alternatively, the inflammatory condition is an allergic inflammatory reaction.

These and other objects and features of the invention will be more fully appreciated when the following detailed description of the invention is read in conjunction with the accompanying FIGURE.

BRIEF DESCRIPTION OF FIGURE

FIG. **1** shows the structures of phenolic compounds and their precursors detected in olive oil: ligstroside (I); oleuropein glucoside (II); aglycone of ligstroside (III); aglycone of oleuropein glucoside (IV); dialdehydic form of ligstroside aglycone laking a carboxymethyl group (V); dialdehydic form of oleuropein glucoside aglycone lacking a carboxymethyl group (VI); tyrosol (VII); hydroxytyrosol (VIII).

DETAILED DESCRIPTION OF THE INVENTION

I. Definitions

Unless otherwise indicated, all terms used herein have the same meaning as they would to one skilled in the art of the present invention. It is to be understood that this invention is not limited to the particular methodology, protocols, and reagents described, as these may vary.

The term "effective amount", as used herein, represents an amount of agent necessary to prevent or treat a subject sus-

ceptible to or suffering from an AIDS-associated neurological condition or an inflammatory response following administration to such subject. The active compound may be effective over a wide dosage range. It will be understood that the amount of the compound actually administered will be determined by a physician, in light of the relevant circumstances including the condition to be treated the age, weight, and response of the individual patient, the severity of the patient's symptoms, and the chosen route of administration.

As used herein, the term "treating" includes prophylaxis of a physical and/or mental condition or amelioration or elimination of the developed physical and/or mental condition once it has been established or alleviation of the characteristic symptoms of such condition.

By "oleuropein" is intended secoiridoid glucoside oleuropein (Structure II in FIG. **1**).

By "tyrosol" is intended 4-hydroxyphenethyl alcohol (Structure VII in FIG. **1**).

By "hydroxytyrosol" is intended 3,4-dihydroxyphenethyl alcohol (Structure VIII in the FIG. **1**).

The term "substantially purified", as used herein, refers to a compound or compounds that are removed from their natural environment, isolated or separated, and are at least 60% free, preferably 75% free, more preferably 85% free, even more preferably 90% free, still more preferably 95% free, and most preferably 99% free from other components with which they are naturally associated.

II. Method of the Invention

The invention includes, in one aspect, a method of treating an AIDS-associated neurological disorder. Another aspect of the invention provides a method of treating inflammation or an inflammation-associated disorder. In practicing the method of the invention, the composition as described below, is preferably formulated as a tablet formulation, is preferably administered orally at a desired dose and dosing schedule.

The method of the invention employs phenolic compounds. Hydroxytyrosol and oleuropein are preferred phenols. The phenolic compounds may be synthesized or extracted and/or purified by methods known to those of skill in the art.

A. Olive-Derived Phenols

Preferably, the phenolic compounds are derived from olives that may be obtained from conventional and commercially available sources such as growers. A number of phenolic compounds are found in olives and olive oil, including relatively apolar, oil soluble phenolic compounds as well as relatively polar, water soluble phenolic compounds. In the context of the present invention both groups are denoted as phenols. Apolar phenols comprise the compounds oleuropein, ligstroside and their aglycons. Polar phenols comprise tyrosol, hydroxytyrosol, caffeic acid and vanillic acid.

The olive-derived phenolic compounds employed herein can be prepared by a number of methods known in the art. The olives may be processed by any suitable means to obtain the compositions described. In one embodiment of the invention, the olives are pressed to obtain a mixture including olive oil, vegetation water, and solid by-products. The phenolic compounds may be obtained directly from the mixture, or the mixture may be fractionated and/or purified to obtain the compounds of the invention. The compositions may be fractionated and/or purified by a number of methods known to those of skill in the art. Exemplary methods for fractionation include partitioning with an organic solvent, high pressure liquid chromatography (HPLC), or the use of supercritical fluids.

Exemplary methods for preparing phenolic compositions derived from olives in accordance with the invention may be found in co-owned U.S. Pat. No. 6,165,475, issued Dec. 26, 2000 and U.S. Pat. No. 6,197,308, issued Mar. 6, 2001, each of which is expressly incorporated by reference herein. An exemplary method for preparing hydroxytyrosol-rich compositions from olive vegetation water is found in co-owned U.S. patent application Ser. No. 09/944,744, filed Aug. 31, 2001, which is expressly incorporated by reference herein. Techniques suitable for concentrating and/or isolating oleuropein from aqueous and aqueous-alcoholic solutions are taught, for example, in U.S. Pat. No. 5,714,150, expressly incorporated herein by reference.

A preferred method of obtaining hydroxytyrosol and/or oleuropein is considered below:

1. Producing Vegetation Water

Preferably, the vegetation water is obtained from pitted olives. The olives processed according to the method disclosed herein may be pitted by any suitable means. Pits in the olives contain tyrosol which is an undesired component in the vegetation water and which may not be appreciably eliminated by the acid treatment described below. The pits may be separated from the pulp manually or in an automated manner as described below. Preferably, such means should be capable of segregating the pits without breaking them, which might otherwise cause higher concentrations of tyrosol in the vegetation water. In another embodiment, hydroxytyrosol is extracted from vegetation water obtained from olives that have not been pitted.

To produce vegetation water, olive pulp from the olives is first pressed to obtain a liquid-phase mixture including olive oil, vegetation water, and solid by-products. Thereafter, the vegetation water is separated from the rest of the liquid phase mixture and collected. Exemplary methods of obtaining vegetation water are described in the above-referenced, co-owned U.S. Pat. Nos. 6,165,475 and 6,197,308, both to R. Crea, each of which are expressly incorporated herein by reference in their entirety.

For purposes of commercial production, it may be desirable to automate various aspects of the invention. In this regard, one embodiment contemplates the use of an apparatus as disclosed in U.S. Pat. Nos. 4,452,744, 4,522,119 and 4,370,274, each to Finch et al., and each expressly incorporated herein by reference. Briefly, Finch et al. teach an apparatus for recovering olive oil from olives. Initially, olives are fed to a pulper that separates the olive pits from the olives to obtain a pitless olive meat. The meat is then taken up by an extraction screw that subjects the meat to an extraction pressure sufficient to withdraw a liquid phase, comprising oil, water and a minor proportion of olive pulp. The liquid phase is collected in a bin and then sent to a clarifying centrifuge that separates the pulp from the liquid phase to obtain a mixture comprising olive oil and vegetation water. A purifying centrifuge then separates the vegetation water and a small proportion of solid matter from the mixture to obtain an olive oil, substantially free of vegetation water, that is collected in a tank.

Additional devices that may be used in practicing the present invention are disclosed in Italian Patent Nos. 1276576 and 1278025, each of which is expressly incorporated herein by reference. As above, these devices can be used to separate the pulp from the pits prior to processing of the crushed olive pulp into oil, water, and solid residues.

2. Conversion of Oleuropein to Hydroxytyrosol

In one aspect of the invention, the oleuropein contained in the vegetation water is converted to hydroxytyrosol. The pH of the vegetation water may be decreased by the addition of

acid (organic or inorganic), and the vegetation water allowed to incubate under conditions which promote hydrolysis of oleuropein to hydroxytyrosol. The sample may then be fractionated to separate hydroxytyrosol from other compounds.

In a preferred embodiment, the added acid is citric acid. The acid is added to the vegetation water to adjust the pH to 1-5, preferably 2-4. Solid citric acid can be added while continuously stirring in an amount of preferably about 25 to 50 pounds of acid per about 1000 liters of vegetation water. The pH of the resulting solution can be monitored, and further addition of acid may be necessary to achieve the desired pH.

The acid may also be an organic or inorganic acid other than citric acid. Exemplary acids which may be used in the present invention include the inorganic substances known as the mineral acids—sulfuric, nitric, hydrochloric, and phosphoric acids—and the organic compounds belonging to the carboxylic acid, sulfonic acid, and phenol groups. The addition of acid to the vegetation water serves several purposes: (i) it stabilizes the vegetation water from rapid oxidation by the air/oxigen; (ii) it prevents fermentation (bacteria) of the vegetation water; and (iii) it hydrolizes the oleuropein, converting it to hydroxytyrosol. In one embodiment, the mixture is allowed to incubate until hydroxytyrosol is 75-90% of the total combination of tyrosol and hydroxytyrosol, and substantially none of the oleuropein in the original mixture remains.

3. Purification of Hydroxytyrosol

Following the conversion of oleuropein to hydroxytyrosol, the vegetation water may be fractionated by a number of methods known in the art. Alternatively, vegetation water may be fractionated prior to treatment with acid.

Vegetation water obtained as described above provides a solution which is rich in low molecular weight polyphenols, particularly hydroxytyrosol and a small amount of tyrosol. The concentration of hydroxytyrosol in the processed water may range from 4-5 grams per liter to 10-15 grams per liter depending upon the degree of dilution during the olive oil extraction. In one embodiment, the invention provides a method of extraction or purification that selectively enriches the content of hydroxytyrosol without the addition of contaminants. Thus, the major polyphenolic component, hydroxytyrosol, is isolated from other members of the polyphenolic family, impurities, suspended solids, tannins, and other molecules contained in the vegetation water. Hydroxytyrosol may therefore be produced in a purity and quantity not readily available by current synthetic or natural extraction methods.

B. Treatment of AIDS-Associated Neurological Conditions

In accordance with the present invention, there are provided therapeutic methods for treating a variety of conditions related to nervous system disorders.

In one aspect, the invention method comprises administering to a subject in need thereof an effective amount of a treatment agent having a weight ratio of hydroxytyrosol to oleuropein of between about 1:1 and about 200:1.

In one embodiment of the invention, the treatment agent is targeted against neurological conditions associated with AIDS. The neurological conditions contemplated for treatment are, in one embodiment, direct or indirect effects of the HIV virus itself. Alternatively, the neurological conditions treated according to the method of the invention are related to opportunistic infections of the nervous system. Preferred AIDS-associated neurological conditions for treatment are as follows:

1. ADC

HIV-1 Associated Dementia, also known as AIDS Dementia Complex (ADC), HIV/AIDS encephalopathy or encephalitis, subacute encephalitis, progressive dementia, HIV/AIDS Related Brain Impairment and AIDS Related Dementia, is a clinical diagnosis based on signs and symptoms of cognitive decline and fine motor dysfunction in the setting of HIV-1 infection, after exclusion of other etiologies. ADC may be progressive or relatively static. In the era of highly-active antiretroviral therapy (HAART), the incidence of fulminant ADC has declined; however, the incidence of a more insidious and protracted dementia, with higher CD4 counts, appears to be increasing (Dore, 1999).

Despite more than a decade of intensive research, the precise pathophysiology of ADC remains elusive. On pathology, atrophy and white matter pallor is observed usually without frank demyelination. Despite widespread scarring (gliosis) and neuronal cell loss, HIV-1 does not directly infect neuronal cells. HIV-1 is found only in macrophages in the brain, and degree of macrophage infiltration, rather than brain viral load, corresponds best to dementia severity (Glass, 1995). Radiographically, the diagnosis is supported by characteristic changes in subcortical and periventricular white matter ("HIV encephalitis"), as well as global cerebral atrophy.

Hence, ADC is considered an "indirect" effect of HIV infection: nervous system injury is driven primarily by the neuroimmunologic host response (Nottet, 1995). While some viral products are neurotoxic in brain cell cultures, it appears that proinflammatory molecules, secreted by or induced by macrophages, are the main effectors of ongoing brain injury. Toxic synergies among viral protein products (viz. Tat) and macrophage-derived cytokines (viz. TNF-α), interleukins (viz. IL-6), and oxygen free-radical reactions (viz. peroxynitrite) appear to lead to enhanced vulnerability to oxidative stress in the AIDS brain, resulting in massive cell death (Shi, 1998; Lipton, 1995).

There is no approved treatment for ADC. Cognitive improvement may be observed with aggressive antiretroviral therapy in some treatment naïve, or under treated, patients with ADC (Cohen, 2001). Pathologic observations indicate that HIV encephalitis remains a common finding (Masliah, 2000). HAART regimens, while perhaps attenuating the severity of dementia, do not appear to prevent HIV-associated brain injury.

The neurological symptoms associated with ADC have been treated with certain drugs that have a number of shortcomings. For example, the psychosis associated with HIV dementia has been treated with haloperidol and thioridazine. Molindone has been used for psychotic and delirious HIV dementia patients. Methylphenidate has been used for treatment of depression associated with ADC. Electro-convulsive therapy has been used for HIV-induced stupor. All of these treatments serve to ameliorate symptoms of ADC. None treat ADC itself.

The conditions treated with the treatment agents include, according to one embodiment of the invention, ADC and the various symptoms with which ADC is associated. An exemplary method of treating ADC is described in Examples 1-3. The treatment agent formulations may be administered to achieve a therapeutic effect and slow or counteract the progression of ADC or they can be administered prophylactically to patients not yet exhibiting ADC but exposed to the HIV virus.

2. HIV-Associated Myelopathy

HIV-associated myelopathy occurs in approximately 20% of patients with late stage AIDS and is clinically characterized by progressive spasticity and loss of proprioception,

predominantly in the lower extremities. Pathologically these findings correlate with vacuolar changes that are most prominent in the posterior and lateral columns of the thoracic spinal cord (termed vacuolar myelopathy) and are morphologically similar to those seen in vitamin B_{12} deficiency (Petito et al, 1985). Autopsy studies have shown that vacuolar myelopathy is found in up to 50% of patients dying with AIDS, with only the more severe cases showing symptoms during life (Dal Pan, 1994).

Thus, according to one embodiment of the invention, HIV-associated myelopathy and the symptoms with which HIV-associated myelopathy is associated are treated.

3. Peripheral Neuropathy

According to another embodiment, this invention provides a therapeutic method for treating a patient suffering from peripheral neuropathy. This method involves administering to the patient an effective peripheral neuropathy-treating amount of one or more of the treating agents or pharmaceutical compositions described. In yet another embodiment, this invention provides a prophylactic method for protecting a patient susceptible to peripheral neuropathy. This method involves administering to the patient an effective peripheral neuropathy prophylactic amount of one or more of the pharmaceutical compositions or treating agents of the invention.

Peripheral neuropathy is a very common and disabling problem encountered in HIV infection. It develops primarily in relatively advanced patients with low CD4 counts, and may be exacerbated by the neurotoxicity of several of the drugs commonly used to treat HIV including DDC, DDI, and D4T. However, it is clear that the viral infection itself results in a typical symmetric, painful, distal sensory neuropathy. This entity almost always presents with variable loss of sensation in the feet and a variety of uncomfortable sensations of swelling, prickling, throbbing or other painful sensations in the feet. This may extend up the legs as it worsens and may eventually start to effect the hands. It occurs in around 20% of AIDS patients, and similar symptoms occur in an even greater number when the drug induced neuropathy is included.

Treatment of neuropathic pain such as is encountered in neuropathy is notoriously difficult. Minimizing neurotoxic drugs, optimizing diet, assuring that there are no contributing vitamin deficiencies (especially B_{12} and thiamine) are important first steps. Alcohol is often a neurotoxin, and continued heavy alcohol use may worsen symptoms. Routine analgesics such as aspirin and ibuprofen generally provide little relief. Even narcotics may not fully relieve this kind of pain.

4. Cytomegalovirus Encephalitis and Radiculomyelitis

Cytomegalovirus is a frequent secondary viral infection in AIDS patients, causing retinitis in up to 40%. Autopsy studies indicate that as many as 20-30% of AIDS patients have CMV encephalitis pathologically, while probably almost 10% develop a clinical neurologic deterioration that is probably the result of CMV. There are two general neurologic syndromes which may occur separately, or in conjunction with each other. The first is the result of CMV attacking the spinal roots and cord resulting in a rapid loss of function of bladder, saddle anesthesia and legs weakness with variable degree of pain and paralysis. The CSF typically has an inflammatory pattern, and sometimes CMV can be cultured from the CSF. Evaluation of the CSF for CMV DNA reveals abundant viral DNA.

The other presentation may mimic a more aggressive form of AIDS dementia complex, with symptoms of dementia developing over just a few weeks time, sometimes associated with cranial nerve abnormalities affecting vision, hearing and balance that would be unusual for HIV alone. The spinal fluid is often bland in this disorder, but CSF PCR for CMV DNA is positive, and strongly supports the diagnosis when such a clinical pattern is seen. This disorder is generally rapidly fatal over a period of just 4-8 weeks. Thus, the conditions treated with the treatment agents and pharmaceutical compositions of the invention include, according to one embodiment, CMV encephalitis and radiculomyelitis.

5. Progressive Multifocal Leukoencephalopathy (PML)

PML is a lethal secondary viral infection mostly occurring in AIDS patients with advanced immunodeficiency. At present, approximately 6% of AIDS patients die with this condition. The JC virus is a ubiquitous virus, able to enter the brain and lytically infect oligodendrocytes (the cells making myelin in the brain). Thus, demyelination of the brain results, causing a wide variety of focal neurologic symptoms including weakness, loss of sensation, visual loss, changes in balance and coordination. Because it is usually relentlessly progressive, severe neurologic disability develops over a period of 2-6 months with death following rapidly from general disability. According to one embodiment of the invention PML is a condition treated with the treatment agents or pharmaceutical compositions described.

6. Other Neurological Diseases

Additional neurological diseases and disturbances contemplated for treatment by the method of the invention include, but are not limited to, Alzheimer's disease; Parkinson's disease; motor neuron diseases such as amyotrophic lateral sclerosis (ALS), Huntington's disease and syringomyelia; ataxias, dementias; chorea; dystonia; dyslinesia; encephalomyelopathy; parenchymatous cerebellar degeneration; Kennedy disease; Down syndrome; progressive supernuclear palsy; DRPLA, stroke or other ischemic injuries; thoracic outlet syndrome, trauma; electrical brain injuries; decompression brain injuries; multiple sclerosis; epilepsy; concussive or penetrating injuries of the brain or spinal cord; brain injuries due to exposure of military hazards such as blast over-pressure, ionizing radiation, and genetic neurological conditions.

By "genetic neurological condition" is meant a neurological condition, or a predisposition to it, that is caused at least in part by or correlated with a specific gene or mutation within that gene; for example, a genetic neurological condition can be caused by or correlated with more than one specific gene. Examples of genetic neurological conditions include, but are not limited to, Alzheimer's disease, Huntington's disease, spinal and bulbar muscular atrophy, fragile X syndrome, FRAXE mental retardation, myotonic dystrophy, spinocerebellar ataxia type 1, dentatorubral-pallidoluysian atrophy, and Machado-Joseph disease.

As described above, presently preferred conditions for treatment in accordance with the present invention include AIDS-associated neurological disorders. An especially preferred condition for treatment in accordance with the present invention includes ADC.

The present invention also relates to combinational therapeutic methods for treating AIDS and AIDS-associated neurological disorders. Combinations of agents contemplated for use in the practice of the present invention are administered to a host in need of such treatment by employing an effective amount of a combination of a least one treating agent useful for the treatment of infectious viral conditions, and at least one AIDS-associated neurological disorder treatment agent as described above. Exemplary HIV antivirals with good CNS penetration include zidovudine, D4T, nevirapine, and abacavir.

C. Oxidative Stress

Use of the treatment agents or pharmaceutical compositions of the invention, according to one aspect, in preparations

to be administrated via different carriers will protect the body against oxidative stress and prevent the outburst of different diseases caused by such oxidative stress.

It is known that free radicals (oxidative stress) of different types are associated with a range of diseases such as ischemic or reperfusion injury, thrombosis and embolism, atherosclerosis, allergic/inflammatory conditions such as bronchial asthma and rheumatoid arthritis, diseases caused by ionizing radiation or ultra violet light, conditions related to neurodegenerative diseases for instance Parkinson's disease and Alzheimer's disease, ageing, apoptosis, necrosis and cirrhosis, cataract, physical stress, diabetes, autoimmune diseases, intoxications, colitis, hematocrosis, neoplasms and toxicity of antineoplastic or immuno suppressive agents diseases, premature aging or consequences of viral or bacterial infections and endogeneous or exogeneous chemicals present in air, food, general environmental contamination or lifestyle related exposure. Lipid peroxidation or DNA-oxidation caused by excess generation of radicals can constitute significant damaging pathways in the above conditions and diseases.

Oxidative stress can be chemically, physically or biologically induced. Chemically induced oxidative stress is caused by a compound which gives rise to a tissue damage. Physically induced stress is caused by e.g. 1) radiation, such as radioactive or ionizing radiation or UV radiation; 2) by physical blockage of blood flow; biologically induced oxidative stress is the defense by the body itself, with over-reaction of oxidases in phagocytes, extra and intra cellular, one example is HIV patients. Other examples are asthma, rheumatoid arthritis, diabetes etc, cf. above.

Different conditions such as inflammations, infections, gamma-radiation, UV radiation and deficiency of vitamins/antioxidants give rise to oxidative stress which leads to the different conditions and diseases stated above.

Thus, the invention includes, in one aspect, a method of treating oxidative stress in a person in need thereof, comprising administering to said subject a pharmaceutically effective amount of substantially purified hydroxytyrosol or a substantially purified mixture of hydroxytyrosol and oleuropein. The oxidative stress condition may be selected from the group consisting of an inflammatory response, coronary heart disease, and AIDS-associated neurological disorders.

D. Biological Testing

The effectiveness of a given phenol in treating an AIDS-associated neurological condition may be determined by methods known in the art.

1. Neuropsychological Testing

Cognitive evaluation of subjects may be determined by methods known in the art. For example, cognitive evaluation of HIV-1 infected patients may be performed using the tests as previously described by Ryan et al. (2001). Briefly, these tests assess member (Rey Auditory Learning Test), psychomotor speed (Trail-making), gross and fine motor functioning (Symbol Digit Substitutions, Grooved Pegboard), abstract thinking (Stroop Coor Interference), and mood (Center for Epidemiological Studies Depression Scale, Profile of Mood States).

The results of the tests may be analyzed to create a Z score by comparing each patient's performance to a mean score based on education- and age-adjusted normative data. An exemplary neuropsychological test is the NPZ-8 test utilized in Example 1 below.

2. Macrophage Activation

HIV is found in macrophages in the brain, and degree of macrophage infiltration corresponds well to dementia severity (Adamson, 1999; Glass, 1995). Blood-borne macrophages and/or CD4+ T lymphocytes can carry the virus into the brain and transport it to perivascular and parenchymal blood-derived macrophages and microglia (Bossi, 1998; Ellis, 1997; Brew, 1996).

Surrogate markers of macrophage activation in serum and/or CSF may be identified by methods known in the art.

3. HIV-1 Viral Load

In one embodiment of the invention, the pharmaceutical composition of the invention is administered to HIV-infected patients in amounts and for a time sufficient to induce a clinically significant decrease in HIV viral load. HIV viral load may be measured by any method known to those of skill in the art. An exemplary method of measuring HIV viral load is by determining the level of HIV-RNA (measured in copies per ml) detectable by PCR in the plasma, serum, and/or CSF of an HIV-infected patient, as described in U.S. Pat. No. 6,309,632.

4. Additional Tests

In one embodiment of the invention, neural cell culture systems or in vivo biological tests may be used for determining the efficacy of the compositions in reversing neurotoxicity which mimics that observed with ADC, as described in International Patent Application WO 97/38684.

Additional tests contemplated by the invention include: measurement of isoprostane F2, a marker of oxidative stress and lipid peroxidate; plasma cholesterol and HDL; and CSF concentration of mono and polyphenol metabolites. Methods for performing these tests are known to those of skill in the art.

E. Treatment of Inflammation or Inflammation-Associated Conditions

As noted above, in accordance with another aspect of the invention, there are provided therapeutic methods for treating a variety of conditions related to inflammation or inflammation-associated disorders.

One role of the inflammatory response serves the purpose of eliminating harmful molecules from the body. A wide range of pathogenic insults can initiate an inflammatory response. These include autoimmune stimuli, infections, allergens, immune response to transplanted tissue, noxious chemicals, toxins, ischemia/reperfusion, hypoxia, and mechanical and thermal trauma. Typically, inflammation is a very localized response that serves to expulse, attenuate by dilution, and isolate the damaging agent and injured tissue. The body's response becomes an agent of disease when it results in inappropriate injury to host tissues in the process of eliminating the targeted agent, or responding to a traumatic insult.

Inflammation is a component of pathogenesis in a number of vascular diseases or injuries, including atherosclerosis. Blake, G J and Ridker, P M (2002) *J Internal Medicine* 252:283-294. The cells involved with inflammation include leukocytes (i.e., the immune system cells—neutrophils, eosinophils, lymphocytes, monocytes, basophils, macrophages, dendritic cells, and mast cells), the vascular endothelium, fibroblasts, vascular smooth muscle cells, and myocytes.

The release of inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) by leukocytes is a means by which the immune system combats pathogenic invasions, including infections. TNF-α stimulates the expression and activation of adherence factors on leukocytes and endothelial cells, primes neutrophils for an enhanced inflammatory response to secondary stimuli and enhances adherent neutrophil oxidative activity. In addition, macrophages/dendritic cells act as accessory cells processing antigen for presentation to lymphocytes. The lymphocytes, in turn, become stimulated to act as pro-inflammatory cytotoxic cells.

Generally, cytokines stimulate neutrophils to enhance oxidative and nonoxidative inflammatory activity. Inappropriate and over-release of cytokines can produce counterproductive exaggerated pathogenic effects through the release of tissue-damaging oxidative and nonoxidative products. For example, TNFα can induce neutrophils to adhere to the blood vessel wall and then to migrate through the vessel to the site of injury and release their oxidative and non-oxidative inflammatory products.

Thus, the method of the present invention includes, in one aspect, a method of treating an inflammatory condition in a subject in need of such treatment. The method includes administering to the subject a pharmaceutically effective amount of substantially purified hydroxytyrosol or a substantially purified mixture of hydroxytyrosol and oleuropein.

The subject may have an inflammatory condition characterized by a detectable clinical symptom or change in a level of a biochemical marker with respect to the normal range of the marker.

A dose of an olive plant extract treatment agent having a weight ratio of hydroxytyrosol to oleuropein of between about 1:1 and about 200:1 is administered to the subject. Preferably, the weight ratio is between about 5:1 and about 100:1. More preferably, the weight ratio is between about 10:1 and about 50:1. The administration is continued until there is observed a return of the marker level to the normal range, a desired, measurable decrease in the level of the marker, or a desired change in the clinical symptom.

The marker or the clinical symptom may include any number of markers or clinical symptoms which are generally known in the art to be associated with inflammation. Preferably, the symptoms and markers are associated with specific types of inflammation. These include (i) the symptoms and markers in joint pain and swelling in the case of joint inflammation; (ii) elevated levels of C-reactive protein in the case of coronary inflammation; (iii) respiratory distress in the case of bronchial inflammation; and (iv) elevated CSF levels of isoprostanes or functional or psychofunctional indicators in the case of neuro-inflammation. The marker may be a cytokine, such as TNF-α, interleukin-1, interleukin-6, and/or interleukin-8. Other markers include corticotrophin, cortisol and/or prolactin.

In the case of joint inflammation, the inflammatory condition may be rheumatoid arthritis, osteoarthritis, and/or other inflammatory conditions involving acute joint inflammation, chronic joint inflammation, or both.

Additional inflammatory conditions that may be treated with the agent or extract of the invention include conditions such as delayed type hypersensitivity reaction, a symptom of psoriasis, an autoimmune disease, organ transplant, pain, fever, or tissue graft rejection. Exemplary autoimmune diseases are Reynaud's syndrome, autoimmune thyroiditis, EAE, multiple sclerosis or lupus erythematosus.

Additional exemplary inflammatory conditions include adult respiratory distress syndrome (ARDS), multiple organ injury syndromes secondary to septicemia or trauma, reperfusion injury of myocardial or other tissues, acute glomerulonephritis, reactive arthritis, dermatoses with acute inflammatory components, acute purulent meningitis or other central nervous system inflammatory disorders, thermal injury, hemodialysis, leukapheresis, ulcerative colitis, Crohn's disease, necrotizing enterocolitis, granulocyte transfusion associated syndromes, cytokine-induced toxicity, asthma, psoriasis, skin sunburn, inflammatory pelvic disease, inflammatory bowel disease, urethritis, uvitis, senusitis, pneumonitis, encephalitis, meningitis, myocarditis, nephritis, osteomyelitis, myositis, hepatitis, gastritis, enteritis, dermatitis, gingivitis, appendicitis, pancreatitis, cholocystitis and cholangititis.

The inflammatory condition may be an acute inflammatory reaction or an allergic inflammatory reaction.

The treatment agent mixture may be prepared by any number of methods known in the art. Preferably, the treatment agent is an extract prepared by the process described in Section II.A. above. A particularly preferable method of preparing the treatment agent involves producing vegetation water from olives; optionally adding acid to the vegetation water in an amount effective to produce a pH between about 1 and about 5; and incubating the acidified vegetation water until a substantial portion, e.g. at least 75%, of oleuropein originally present in the vegetation water has been converted to hydroxytyrosol.

A wide variety of administration methods are contemplated by the present invention and discussed in further detail in Section III below. These include oral delivery, intramuscular injection, intravenous injection, transdermal delivery, and transmucosal delivery. Oral delivery is preferred.

The compounds of this invention are useful in the treatment or alleviation of inflammation, other inflammation associated disorders, such as arthritis, neurodegeneration and colon cancer, in mammals, preferably humans, dogs, cats or livestock animals.

The amount of therapeutically active compound that ss administered and the dosage regimen for treating a disease condition with the compounds and/or composition of this invention depends on a variety of factors, including the age, weight, sex and medical condition of the subject, the severity of the disease, the route and frequency of administration, and the particular compound employed, and thus may vary widely. The pharmaceutical compositions may contain active ingredient in the range of about 0.1 to 2000 mg/kg body weight, preferably in the range of about 0.3 to 50 mg/kg and most preferably about 0.6 mg/kg. A daily dose can be administered in one to four doses per day. In one embodiment a daily dose of 20 mg is delivered in 4 doses of 5 mg each.

The active agent or extract of the present invention may be administered in combination with other agents. The agents may be administered before, after, and/or during administration with the primary treatment agent. Preferable combinatorial agents include glucosamine sulfate, chondroitin sulfate, sea cucumber extract, hydrolyzed shark cartilage, collagen II, and methylsulfonylmethane.

Additional inhibitors of mediators of inflammation contemplated for use in combination with the active agent or extract of the present invention include matrix metalloproteinase inhibitors, aggrecanase inhibitors, TACE inhibitors, leucotriene receptor antagonists, IL-1 processing and release inhibitors, IL-1 ra, H (1)-receptor antagonists; kinin-B (1)- and B (2)-receptor antagonists; prostaglandin inhibitors such as PGD-, PGF-PGI (2)-, and PGE-receptor antagonists; thromboxane A (2)(TXA2-) inhibitors; 5- and 12-lipoxygenase inhibitors; leukotriene LTC (4)-, LTD (4)/LTE (4)-, and LTB (4)-inhibitors; PAF-receptor antagonists; gold in the form of an aurothio group together with various hydrophilic groups; immunosuppressive agents, e.g., cyclosporine, azathioprine, and methotrexate; anti-inflammatory glucocorticoids; penicillamine; hydroxychloroquine; anti-gout agents, e.g., colchicine, xanthine oxidase inhibitors, e.g., allopurinol, and uricosuric agents, e.g., probenecid, sulfinpyrazone, and benzbromarone.

III. Pharmaceutical Compositions

The therapeutic compositions described herein may be administered subcutaneously, intravenously, parenterally,

intraperitoneally, intradermally, intramuscularly, topically, enteral (for example, orally), rectally, nasally, buccally, vaginally, by inhalation spray, by drug pump or via an implanted reservoir in dosage formulations containing conventional nontoxic, physiologically (or pharmaceutically) acceptable carriers or vehicles.

In a specific embodiment, it may be desirable to administer the agents of the invention locally to a localized area in need of treatment; this may be achieved by, for example, and not by way of limitation, local infusion during surgery, topical application, transdermal patches, by injection, by means of a catheter, by means of a suppository, or by means of an implant, said implant being of a porous, non-porous, or gelatinous material, including membranes; such as sialastic membranes or fibers.

When it is desirable to direct the drug to the central nervous system, techniques which can opportunistically open the blood brain barrier for a time adequate to deliver the drug there through can be used. For example, a composition of 5% mannitose and water can be used. The present invention also provides pharmaceutical compositions. Such compositions comprise a therapeutically (or prophylactically) effective amount of the agent, and a physiologically acceptable carrier or excipient. Such a carrier includes, but is not limited to, saline, buffered saline, dextrose, water, glycerol, ethanol, and combinations thereof. The carrier and composition can be sterile. The formulation should suit the mode of administration.

Suitable pharmaceutically acceptable carriers include but are not limited to water, salt solutions (for example, NaCl), alcohols, gum arabic, vegetable oils, benzyl alcohols, polyethylene glycols, gelatin, carbohydrates such as lactose, amylose or starch, magnesium stearate, talc, silicic acid, viscous paraffin, perfume oil, fatty acid esters, hydroxymethylcellulose, polyvinyl pyrolidone, etc. The pharmaceutical preparations can be sterilized and if desired, mixed with auxiliary agents, for example, lubricants, preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing osmotic pressure, buffers, coloring, flavoring and/or aromatic substances and the like which do not deleteriously react with the active compounds.

The compositions, if desired, can also contain minor amounts of wetting or emulsifying agents, or pH buffering agents. The composition can be a liquid solution, suspension, emulsion, tablet, pill, capsule, sustained release formulation, or powder. The composition can be formulated as a suppository, with traditional binders and carriers such as triglycerides. Oral formulation can include standard carriers such as pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, polyvinyl pyrollidone, sodium saccharine, cellulose, magnesium carbonate, etc.

The compositions can be formulated in accordance with the routine procedure as a pharmaceutical composition adapted for intravenous administration to human beings. Typically, compositions for intravenous administration are solutions in sterile isotonic aqueous buffer. Where necessary, the composition may also include a solubilizing agent and a local anesthetic to ease pain at the site of the injection.

Generally, the ingredients are supplied either separately or mixed together in unit dosage form, for example, as a dry lyophilized powder or water free concentrate in a hermetically sealed container such as an ampoule or sachette indicating the quantity of active agent. Where the composition is to be administered by infusion, it can be dispensed with an infusion bottle containing sterile pharmaceutical grade water, saline or dextrose/water. Where the composition is administered by injection, an ampule of sterile water for injection or saline can be provided so that the ingredients may be mixed prior to administration.

For topical application, there are employed as nonsprayable forms, viscous to semi-solid or solid forms comprising a carrier compatible with topical application and having a dynamic viscosity preferably greater than water. Suitable formulations include but are not limited to solutions, suspensions, emulsions, creams, ointments, powders, enemas, lotions, sols, liniments, salves, aerosols, etc., which are, if desired, sterilized or mixed with auxiliary agents, for example, preservatives, stabilizers, wetting agents, buffers or salts for influencing osmotic pressure, etc. The drug may be incorporated into a cosmetic formulation. For topical application, also suitable are sprayable aerosol preparations wherein the active ingredient, preferably in combination with a solid or liquid inert carrier material, is packaged in a squeeze bottle or in admixture with a pressurized volatile, normally gaseous propellant, e.g., pressurized air.

The amount of agent or agents which will be effective in the treatment of a particular disorder or condition will depend on the nature of the disorder or condition, and can be determined by standard clinical techniques. In addition, in vitro or in vivo assays may optionally be employed to help identify optimal dosage ranges. The precise dose to be employed in the formulation will also depend on the route of administration, and the seriousness of the disease or disorder, and should be decided according to the judgment of the practitioner and each patient's circumstances.

From the foregoing, it can be seen how various objects and features of the invention are met.

IV. EXAMPLES

The following examples further illustrate the invention described herein and are in no way intended to limit the scope of the invention.

Example 1

Study Procedures

This is a prospective, randomized, double-blind, placebo-controlled six-week parallel study of up to 32 subjects with HIV-associated cognitive dysfunction who have been on a stable medication regimen (antiretroviral and other medications) for at least 8 weeks. Subjects will be stratified at randomization, based on a "biased coin" paradigm, with regard to HIV-1 Viral Load <50,000 copies/ml versus equal to or greater than 50,000 copies/ml, to insure the two groups are balanced with regard to this important clinical variable. Subjects will receive either the active ingredient (20 mg total phenols) or identical placebo tablets (provided by the manufacturer) to be taken orally. Subject, Investigator and Sponsor will be blinded to treatment assignment until study completion.

At baseline and at Study Week 6, neuropsychiatric testing (NPZ-8), neurological examination, urinary F2 Isoprostane, serum beta-2 microglobulin, HIV-1 Viral Load, CD4 lymphocyte count, serum chemistries (electrolytes, renal and liver function tests), coagulation profile, and lipid profile will be obtained. Approximately 15 mL of blood will be obtained at baseline and at 6 weeks from each subject. A urine sample of 20 mL will be obtained at these time points. At study weeks 2 and 4, subjects will be contacted by the study assistant by

telephone with regard to any changes in status or adverse events. Adverse events will be evaluated by the PI as appropriate.

It is anticipated that up to 8 subjects will consent to lumbar puncture at baseline and at 6 weeks for assessment of CSF F2 Isoprostane, B2 microglobulin, CSF viral load, and measurement of Hydroxytyrosol-derived metabolites. LP will be performed by the PI.

The PI, for example, a board-certified neurologist, neuroAIDS specialist and PI in previous ADC trials, will perform patient selection and neurologic examinations. The neuropsychiatric battery, the NPZ-8, takes about 30 minutes to administer, and has been validated in the ADC population and is the most commonly used instrument in ADC treatment trials. The neurologic examination will take approximately 30 minutes. The baseline and follow-up visits should take no more than 90 minutes each, including phlebotomy, for the average subject. Each follow-up telephone call will take, on average, approximately 10 minutes.

Urinary and, if available, CSF F2-isoprostane assays will be performed at a state-of-the-art laboratory which performs this and other prostaglandin assays. CSF phenol (hydroxytyrosol) concentrations will be measured, blind to treatment assignment of subjects

Subjects willing to undergo baseline and follow-up lumbar puncture will be consented separately. No subject will be denied participation in the study because of reluctance to undergo LP. The procedure typically takes 20 minutes. Subjects can, if they wish, remain supine for a period of time after the procedure. However, contrary to common belief, remaining supine post LP is not associated with reduction in incidence (10%) of post LP headache. Should a post LP headache occur, the subject will be offered treatment (blood patch: >85% success rate).

Example 2

Data Analysis

Safety data will be summarized descriptively for the two groups—active vs. placebo—using COSTART terms for mapping adverse events.

Change scores in laboratory safety evaluations (serum electrolytes, BUN, creatinine, CBC and differential, PT, PTT, platelets, total and HDL cholesterol, AST, ALT, total bilirubin) will be summarized.

The primary efficacy variable—difference in group mean concentrations of Isoprostane F2 at Study Week 6 compared with baseline—will be analyzed using 2-sided student's T test, with normalization of baseline concentrations. Because a normal distribution of this variable cannot be assumed, a Wilcoxin signed rank test will also be used to examine the difference in Iso-F2 from baseline to Study Week 6 in individual subjects, ranked according to magnitude, with determination of the test statistic to compare the treatment versus placebo groups. With regard to secondary variables, these approaches will be used to examine differences from baseline in B2 microglobulin and HIV-1 viral load in serum and, where possible, in urine. Descriptive summary statistics will be provided for subgroups. All analyses will be done by an independent third party using SAS software.

Example 3

Subject Selection

All subjects will be HIV-1 seropositive by Elisa, confirmed by Western Blot. Rationale for studying this population: there is no proven treatment for ADC or HIV-associated cognitive motor syndrome. The brain injury that occurs as a result of HIV-1 infection continues to afflict AIDS patients, despite highly-active antiretroviral therapy. As HIV-1 infected individuals live longer, ADC prevalence, and perhaps incidence, will likely rise.

Up to 32 subjects will be enrolled. It is expected that full data will be then available for approximately 12 subjects in each group, talking into account a 20% drop out rate typical from an ADC clinical trial. The sample size is reasonable for a pilot safety and tolerability study. Statistical significance is not expected for the primary efficacy endpoint in this small study; a trend towards group differences may be detected.

HIV-1 seropositive men and women over the age of 18, with signs and symptoms of HIV-associated cognitive-motor syndrome or frank ADC (Stage 0.5-2 Memorial Sloan Kettering AIDS Dementia Scale) for at least 3 months, and a Karnovsky score >50 (able to care for most of daily needs, but may need some assistance) will be eligible for enrollment. Subjects will have been on a stable regimen of antiretroviral and any other medical treatments for at least 3 months, and will reasonably be expected to remain on their current regimen for the duration of the study. Subjects in other investigational protocols or agents will be excluded. Other causes of cognitive impairment, such as thyroid disease, vitamin deficiency, testosterone deficiency (if male), neurosyphilis, other CNS disease, uncontrolled epilepsy, untreated depression, hepatic or uremic encephalopathy, traumatic brain injury or drug or alcohol abuse will be excluded per standard evaluation prior to enrollment. If an appropriate workup has not been performed, the potential subject will be referred back to his or her primary provider for evaluation. Subjects will be ambulatory, and have no active clinically significant systemic disease (other than HIV) that would, in the PI's judgment, preclude safe participation or compliance with the protocol.

Initial results from the above examples 1-3 showed a statistically significant favorable change in 8-isoprostane levels in the urine.

Example 4

Arthritis Studies

Test a group of individuals with Rheumatoid Arthritis and a group with Osteoarthritis with the stress reactivity protocol, before and after 4 weeks of active agent (20 mg total phenols) supplementation and compare to controls over the same time period with no supplementation. Measurements will include heart rate, blood pressure, cortisol, ACTH, PRL, cytokines, and CRP.

Test individuals with Rheumatoid Arthritis, before and after 10 weeks of active agent supplementation and compare to a group doing water aerobic exercise and a control group that does no intervention. Measurements will include assessment of disease activity, prostaglandins, cortisol, PRL, CRP, mood changes, fitness measures, and endurance.

Test individuals with Rheumatoid Arthritis, with and without active agent supplementation for four weeks, and examine their acute phase response to an exercise strength test using a leg press set at 70% of the 1 Rep Max. Measurements will include cortisol, PRL, CRP, and a panel of inflammatory cytokines.

Evaluate increasing concentrations of active agent in a collagent-induced arthritis mouse model at 1.3 mg, 13 mg and 130 mg/mouse; with and without Cox-2 inhibitors. The positive control involves treatment with Cox-2 inhibitors, NSAID, or steroids at the highest dose levels. Parameters

such as swelling determined by ankle width measurement; histopathological score involving subsynovial inflammation characterized by mononuclear cell resembling nodule formation, pannus formation, bone erosion and synovial hyperplasia; radiological score; and cytokine analysis score measuring levels of TNF-α, IL-1, JE/CCLE (mouse Monococyte Chemotactic Protein-1), and IL-8.

Use of the mouse model as an acute inflammation/injury model to evaluate inhibitors that increase survival by reducing the levels of TNF-α and IL-1 induced by a single intraperitoneal injection of 50 μg of LPS and D-Galactosamine (600 mg/kg). In this model, mice are treated with the active agent (1.3; 13; and 130 mg/mouse) 12 hours prior to injection with LPS/D-Gal i.p. Survivial of mice is followed for 72 hours following injection with LPS/D-Gal. At 72 hours, blood is collected from all mice by retro-orbital puncture for measurement of TNF-α and IL-1 levels by ELISA.

Additional exemplary studies include TNF-α and IL-1 production induced by LPS by THP-1 monocytes, IL-8 production by fibroblasts; the effects of the active agent on the levels of superoxide and hydrogen peroxide production from human neutrophils; and basal levels of Cox-1 and LPS-induced levels of Cox-2 regulation in monocytes and fibroblasts with active agent added prior to LPS addition.

All publications and patent applications mentioned in this specification are indicative of the level of skill of those skilled in the art to which this invention pertains. All publications and patent applications are herein incorporated by reference to the same extent as if each individual publication or patent application was specifically and individually indicated to be incorporated by reference.

Although the invention has been described with respect to particular embodiments, it will be apparent to those skilled in the art that various changes and modifications can be made without departing from the invention.

It is claimed:

1. A method of treating a subject having an inflammatory condition characterized by a detectable clinical symptom or change in a level of a biochemical marker with respect to the normal range of the marker, the method comprising:

administering to the subject a dose corresponding to between about 0.1 mg/kg body weight and 2000 mg/kg body weight daily of a first treatment agent comprised of an olive plant extract having a weight ratio of hydroxytyrosol to oleuropein of between about 1:1 and about 200:1; and

continuing said administration until there is observed a return of the marker level to the normal range or a desired change in the clinical symptom,

where the marker or the clinical symptom is selected from the group consisting of

(i) elevated levels of C-reactive protein in the case of coronary inflammation;

(ii) respiratory distress in the case of bronchial inflammation; and

(iii) elevated CSF levels of isoprostanes or clinical symptoms determined from neuropsychological testing in the case of neuro inflammation.

2. The method of claim **1**, wherein said weight ratio is between about 5:1 and about 100:1.

3. The method of claim **2**, wherein said weight ratio is between about 10:1 and about 50:1.

4. The method of claim **1**, wherein said administering comprises a method selected from the group consisting of oral delivery, intramuscular injection, intravenous injection, transdermal delivery, and transmucosal delivery.

5. The method of claim **4**, wherein said administering comprises oral delivery.

6. The method of claim **1**, wherein said administering further comprises administering a second disease treatment agent.

7. The method of claim **6**, wherein said administering of the second treatment agent is before or after administration of the first treatment agent.

8. The method of claim **6**, wherein said administering of a second treatment agent is coincident with administering the first treatment agent.

9. The method of claim **6**, wherein the second treatment agent comprises one or more of the components selected from the group consisting of glucosamine sulfate, chondroitin sulfate, sea cucumber extract, hydrolyzed shark cartilage, collagen II, and methylsulfonylmethane.

10. The method of claim **1**, wherein the agent is administered at a dosage of between about 0.3 mg/kg and 1 mg/kg per day.

11. The method of claim **10**, wherein the agent is administered at a dosage of about 0.6 mg/kg per day.

12. The method of claim **1**, wherein said subject is a human.

13. The method of claim **1**, wherein said agent is dried to provide a powder extract.

14. The method of claim **1**, wherein said agent is in the form of a tablet, capsule, or pill.

15. The method of claim **1**, wherein said agent is in the form of a liquid or liquid drops.

16. A method of treating an inflammatory condition in a subject in need of such treatment, comprising administering to said subject a dosage amount corresponding to between about 0.1 mg/kg body weight and 2000 mg/kg body weight daily of substantially purified hydroxytyrosol or a substantially purified mixture of hydroxytyrosol and oleuropein, wherein said inflammatory condition is in response to a condition selected from the group consisting of: delayed type hypersensitivity reaction, psoriasis, an autoimmune disease, organ transplant, pain, fever, and tissue graft rejection.

* * * * *

CERTIFICATE OF SERVICE

The undersigned hereby certifies that on March 10, 2014, a copy of the foregoing document:

BRIEF FOR PLAINTIFF-APPELLANT CREAGRI, INC.

was filed electronically with the Clerk of the Court using the Appellate CM/ECF System, which will send a Notice of Docket Activity via electronic mail to all counsel of record. Additionally, a copy of the foregoing document was served upon counsel for Defendant-Appellee via electronic mail listed below:

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CERTIFICATE OF COMPLIANCE WITH RULE 32(A)

1. This brief complies with the type-volume limitation of Fed. R. App. P. 32(a)(7)(B) because this brief contains 13,977 words, exclusive of the certificate of interest, table of contents, table of citations, statement of related cases, addendum and this certificate of compliance as exempted by Fed. R. App. 32(a)(7)(B)(iii) and Fed. Cir. R. 32(b).

2. This brief complies with the typeface requirements of Fed. R. App. P. 32(a)(5) and the type style requirements of Fed. R. App. P. 32(a)(6) because this brief has been prepared in a proportionally spaced typeface using Microsoft Word 2007 in Times New Roman 14 point font.

Dated: March 10, 2014

Respectfully submitted,

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